



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 72

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 72

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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# Contents

CONTRIBUTORS .....	vii
PREFACE .....	ix

## Five- and Six-Membered Heteroaromatic Compounds as $\sigma$ and $\pi$ Ligands

A. D. GARNOVSKII AND A. P. SADIMENKO

I. Introduction. ....	1
II. Types of Heteroaromatic Ligands and Their Complexes .....	2
III. Methods of Synthesis of $\sigma$ - and $\pi$ -Complexes of Five- and Six-Membered Hetarenes .....	4
IV. Structures of Complex Compounds from Five- and Six-Membered Hetarenes .....	15
V. Conclusion .....	49
References .....	50

## Synthesis of Amino Derivatives of Five-Membered Heterocycles by Thorpe-Ziegler Cyclization

VLADIMIR G. GRANIK, ALEXANDER V. KADUSHKIN, AND JÜRGEN LIEBSCHER

I. Introduction. ....	79
II. Synthesis of 3-Aminofurans. ....	80
III. Synthesis of 3-Aminopyrroles .....	85
IV. Synthesis of 3-Aminothiophenes .....	96
V. Synthesis of 3-Aminoselenophenes .....	111
VI. Synthesis of Aminoazoles .....	113
References .....	116

1,2,4,-Triazolo- and Tetrazolo[*x,y-z*]pyrimidines

E. S. H. EL ASHRY AND N. RASHED

I. Introduction . . . . .	127
II. 1,2,4-Triazolo[ <i>x,y-z</i> ]pyrimidines . . . . .	127
III. Tetrazolo[ <i>x,y-z</i> ]pyrimidines . . . . .	202
References . . . . .	211

Chemistry of Pyrido[2,1-*b*][1,3]oxazines, Pyrido[2,1-*b*][1,3]thiazines,  
and Their Benzologs, Part IV

ISTVÁN HERMECZ

I. Introduction . . . . .	225
II. Structure . . . . .	226
III. Reactivity . . . . .	234
IV. Synthesis . . . . .	253
V. Applications and Important Compounds . . . . .	271
References . . . . .	275

## Enamines as Synthons in the Synthesis of Heterocycles

VLADIMIR G. GRANIK, VADIM A. MAKAROV, AND CYRIL PÁRKÁNYI

I. Introduction . . . . .	283
II. Formation of Small Rings . . . . .	284
III. Five-Membered Rings . . . . .	284
IV. Six-Membered Rings . . . . .	306
V. Synthesis of Seven- and Eight-Membered Rings . . . . .	338
VI. Enamines as Electron-Rich Synthons in Reactions with Electron-Deficient Azadienes . . . . .	340
VII. Conclusion . . . . .	346
References . . . . .	346

## Fragmentations of Five-Membered Rings

PAUL RADEMACHER

I. Introduction . . . . .	361
II. Fragmentation of Five-Membered Rings: Overview . . . . .	364
III. [5 → 5] Isomerizations . . . . .	367
IV. [5 → 4 + 1] Fragmentations . . . . .	369
V. [5 → 3 + 2] Fragmentations . . . . .	370
VI. [5 → 2 + 2 + 1] Fragmentations . . . . .	398
VII. [5 → 2 + 1 + 1 + 1] and [5 → 1 + 1 + 1 + 1 + 1] Fragmentations . . . . .	404
VIII. Conclusions . . . . .	404
References . . . . .	406

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## Preface

Volume 72 of *Advances in Heterocyclic Chemistry* consists of six chapters. The first considers the role of five- and six-membered heteroaromatic compounds as  $\sigma$  and  $\pi$  ligands. Authored by Professors A. D. Garnovskii (Rostov-on-Don, Russia) and A. P. Sadimenko (Fort Hare, South Africa), it gives an overview of the multitude of structural types that can arise when heterocycles are used as ligands in organometallic derivatives. Many such compounds are of great industrial importance in catalytic and other processes. No previous comprehensive overview of this subject has been available.

The second chapter, by Drs. V. G. Granik and A. V. Kadushkin (Moscow, Russia) and Professor J. Liebscher (Berlin, Germany), covers the synthesis of amino derivatives of heterocycles by the Thorpe-Ziegler cyclization of cyanides. The chapter concentrates on work that appeared from 1983 to 1996 and extends earlier reviews.

The third chapter in this volume, by Professor E. S. H. El Ashry and Professor N. Rashed (Alexandria, Egypt), provides an overview of 1,2,4-triazolo- and tetrazolopyrimidines and complements the review in Volume 71 of our series by the same authors, which dealt with 1,2,3-triazolopyrimidines. Again, all of these compound classes have received much attention recently as potential therapeutic agents.

The next chapter continues the series by Dr. I. Hermecz (Budapest, Hungary) on the chemistry of pyridooxazines and -thiazines. This chapter, Part IV of the series, deals with the chemistry of pyrido[2,1-*b*][1,3]oxazines and [1,3]thiazines together with their benzologs. The first three parts of the series comprised Part I in Volume 69 on pyrido[1,2-*b*]-1,2-oxazines, -1,2-thiazines, and -pyridazines and their benzologs; Part II in Volume 70 on pyrido[1,2-*c*]-1,3-oxazines, -1,3-thiazines, and -pyrimidines and their benzologs; and Part III in Volume 71 on pyrido[2,1-*c*]-1,4-oxazines, -1,4-thiazines, and -pyrazines and their benzologs.

A chapter authored by Drs. V. G. Granik and V. A. Makarov (Moscow, Russia) together with Dr. Cyril Párkányi (Florida Atlantic University)

covers the use of enamines as synthons. This chapter provides, in condensed format, an overview of the very large number of possible applications of enamines in heterocyclic synthesis.

The final chapter in this volume, by Professor P. Rademacher (Essen University, Germany), reviews possible pathways for fragmentations of five-membered rings. Such fragmentations have been induced by a variety of methods and in this first systematic treatment of the subject are classified according to the bonds broken.

ALAN R. KATRITZKY

# Five- and Six-Membered Heteroaromatic Compounds as $\sigma$ and $\pi$ Ligands

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*Dedicated to the 70<sup>th</sup> anniversary of Alan R. Katritzky, the founder of  
organometallic and coordination chemistry of heterocycles.*

I. Introduction . . . . .	1
II. Types of Heteroaromatic Ligands and Their Complexes . . . . .	2
III. Methods of Synthesis of $\sigma$ - and $\pi$ -Complexes of Five- and Six-Membered Hetarenes . . . . .	4
A. Direct Interaction of Components . . . . .	4
B. Ligand Exchange . . . . .	5
C. Synthesis of Hetarene Complexes from the Zero-Valent Metals . . . . .	9
D. Synthesis of Hetarene Metal Chelates . . . . .	10
E. Other Methods of Synthesis of Hetarene Complexes . . . . .	13
IV. Structures of Complex Compounds from Five- and Six-Membered Hetarenes . . . . .	15
A. Complexes of Five-Membered Heterocycles with One Heteroatom . . . . .	15
B. Complex Compounds of Azines and Their Phosphorus- and Arsenic-Containing Analogs . . . . .	20
C. Coordination Compounds of Azoles . . . . .	24
D. Complexes of Five- and Six-Membered Hetarenes Containing Endocyclic Elements of Groups III–IV . . . . .	32
E. Complexes of Hetarenes Containing Exocyclic Coordination-Active Substituents . . . . .	34
V. Conclusion . . . . .	49
References . . . . .	50

## I. Introduction

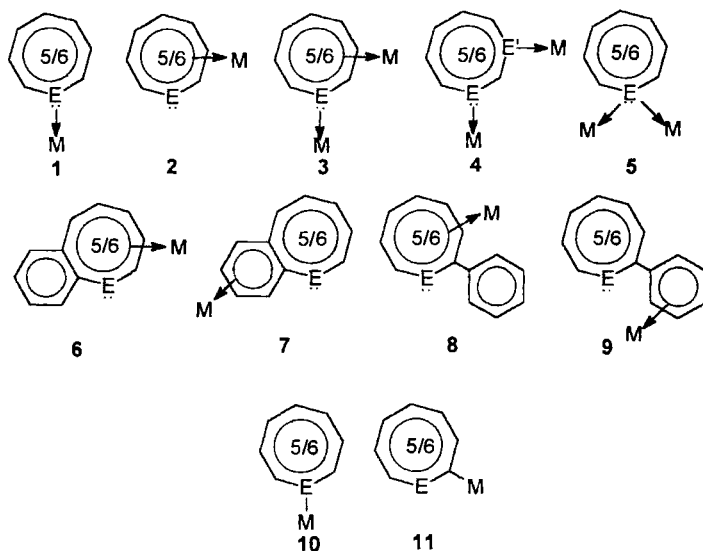
Among the chemical properties of heteroaromatic compounds, complex-forming reactions are important. However, they have been described incompletely (96MI1; 97AHC). Complex-forming reactions have been presented in thousands of papers. Their account is beyond the limits of this review. Other reviews are devoted both to the general problems of the

coordination chemistry of heteroaromatic ligands [73RCR89, 73UK177; 78JHC1057; 83KGS1155, 83KGS1299; 87MI1; 93CCR237; 95MI1; 97RCR389, 97UK434; 98CCR(ip)] and to separate classes of heteroarenes: pyrrole (96MI15), thiophene (90CCR61), phosphole (88CRV429; 94CCR1), pyrazole [71ACR17; 72CRV497, 72UK1660; 86PIC115; 87MI2; 92CCR325; 93CRV943; 95MI2, 95NJC551; 96CCR(147)247, 96MI2], imidazole and benzimidazole (74CRV471; 96MI3), triazoles (88AIC171), tetrazole (69CCR463), and isoxazole (79AHC147; 91CCR251). We therefore consider basic trends without covering the subject exhaustively.

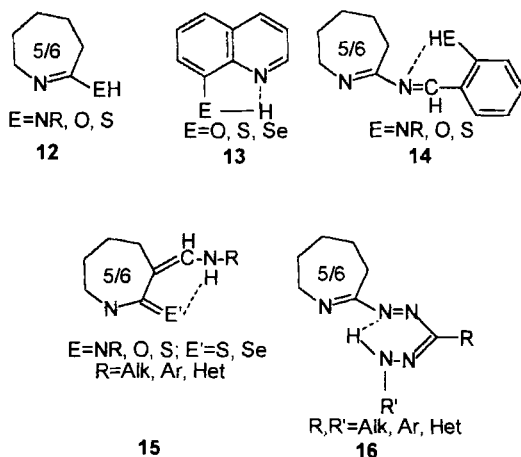
Our focus is the interaction of metals with donor sites of the heteroaromatic ligands, including heteroatoms ( $\sigma$ -complex formation) and the  $\pi$ -system of the heteroring ( $\pi$ -complex formation). It has long been accepted that metal binding occurs, as in quaternization, exclusively at the pyridinic N atoms of nitrogen-containing five- and six-membered heterocycles and is merely an example of the localized coordination bond. Less appreciated is the fact that as classical aromatic ligands [93AHC(56)303], heteroaromatic compounds form  $\eta^n$ -complexes at the expense of the  $\pi$ -donor function. Simultaneous participation of the  $\sigma$ - and  $\pi$ -donor sites in coordination is least common. The same is true for the bonding of a heteroatom to several metals. Finally, inclusion or annelation of a heteroaromatic system to a chelating ligand often leads to substantial changes in their stereochemistry and stereodynamics compared to those for the analogous aliphatic and aromatic ligands.

## II. Types of Heteroaromatic Ligands and Their Complexes

Five- and six-membered heteroaromatic ligands are common. They contain several donor sites, heteroatoms (the elements of V and VI Groups, E), and the  $\pi$ -system. They are classified as ambidentate  $\sigma, \pi$ -donor ligands (86MI1) and may form two types of complex compounds: the common  $\sigma$ -(**1**) and the less-common  $\pi$ - (**2**) complexes. In these and subsequent structures, (**3**–**5**), E = N, P, As, Sb; O, S, Se, Te. It is possible to prepare binuclear  $\sigma, \pi$ -complexes when both donor sites take part in coordination (**3**). Bi- and polynuclear structures, e.g., **4**, are formed based on heteroaromatic ligands containing several donor sites. The ligands also fulfill a bridging function (93CCR319). Metal complexes in which the donor site of a ligand (E) may be bonded simultaneously to several metal atoms (**5**) are rare. If a heterocycle contains several aromatic fragments, a  $\pi, \pi$ -competitive coordination may arise, as illustrated by **6**–**9**. Other metal  $\sigma$ -bonded structures are the E–M (**10**) and C–M (**11**) derivatives (72JA3370; 86UK1495; 93CRV1243).



Introduction of a coordination-active substituent on the heterocycle leads to new  $\sigma, \pi$ -donors and hetaryl-containing ligands. The representatives of the first group are 2-amino-, 2-hydroxy-, and 2-mercapto derivatives (**12**) and similar 8-substituted derivatives of quinoline (**13**) (94MI1). Representatives of the second group are the azomethine ligands **14** and **15** (93CCR1, 93MI6), and hetarylformazanes (**16**) (75UK1052; 92MI1).

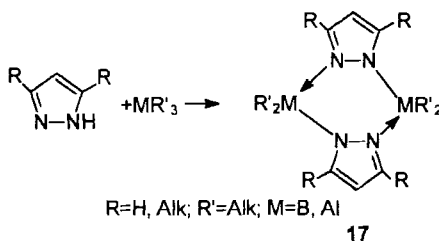


### III. Methods of Synthesis of $\sigma$ - and $\pi$ -Complexes of Five- and Six-Membered Heteroarenes

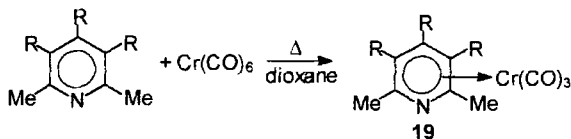
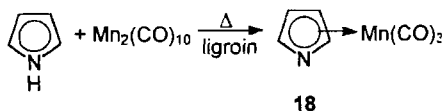
Synthetic methods for the preparation of coordination compounds of heterocycles are considered in the majority of references given earlier and elsewhere (74MI1; 82MI3; 95MI8).

#### A. DIRECT INTERACTION OF COMPONENTS

The basic method of synthesis of  $\sigma$ - and  $\pi$ -complexes is the direct interaction of ligands and metal species (salts, carbonyl, etc.). This method is described by a reaction equation  $mL + MX_n \rightarrow L_m \cdot MX_n$ , and is applied to prepare complexes (**1**) of azoles (80KK3) and azines (95MI8). For azoles, this synthetic approach has been considered in detail (73RCR89, 73UK177). Preparation of complexes is often conducted in nonaqueous media (alcohols, acetone, halocarbons). The composition of the products depends on the ratio of the reactants and ranges from 1 to 6 ( $m$ ). The nature of L and X determines the value of  $m$ . Bulky substituents, especially those proximate to the donor sites E, lead to a decrease of  $m$ . The same effect is observed on transition from the  $BF_4^-$  and  $ClO_4^-$  to  $NO_3^-$  and  $NCY^-$  ( $Y = O, S, Se$ ) anions. Synthesis of complexes having a low value of  $m$  may be accomplished by vacuum decomposition of compounds containing a larger number of ligands. The basicity ( $pK_a$ ) of azoles influences the coordination number of metals only weakly. Thus, complexes containing from one to six ligands may be prepared for strong (imidazole and benzimidazole) and weak (tetrazole and isoxazole) bases. However, the influence of basicity on the composition is pronounced in a series of benzazoles. For benzimidazole ( $pK_a = 5.53$ ), it is easy to prepare the complexes  $L_4MX_2$ . For benzothiazole ( $pK_a \approx 2$ ), complex compounds of this composition can be prepared for a limited number of metals and anions. Benzoxazole forms complexes containing no more than two ligands. The structure of a ligand influences not only the composition but also the type of  $\sigma$ -complex. Thus, azoles containing free NH groups and having a high acidity may yield not only **1** but also **10**. The latter are typical for tetrazole. Formation of **1** or **10** depends not only on the acidity of the NH groups, but also on the nature of the  $MX_n$  reagents. Thus, if metal salts afford adducts (**1**) of composition  $L_m \cdot MX_n$ , the interaction of azoles with  $MR_3$  is followed by the N-organometallic derivatives of azoles (**10**). The transformation (72ZOB920) leading to the metallocyclic structures (**17**) is illustrative.



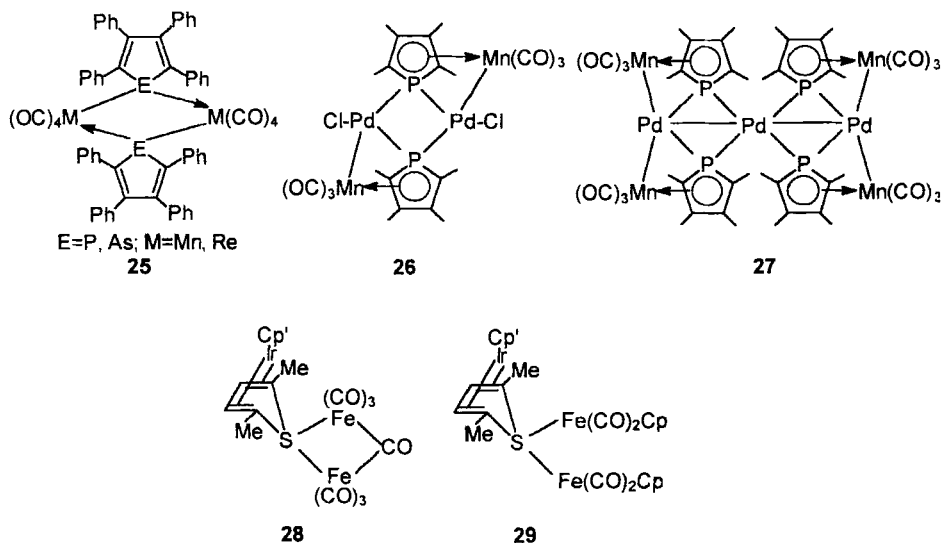
This synthetic method is applied to the preparation of  $\sigma, \sigma'$ -complexes (**4**), among them, the bridging structures based on pyrazole, imidazole [90ICA(173)247; 93IC888], and diazines (92MI2; 93CRV847). Direct interaction is applied to the synthesis of  $\pi$ -complexes (**2**). Such reactions occur between ligands and metal carbonyls in nonaqueous media, e.g., **18**. Another illustration is the preparation of one of the first  $\eta^6$  ( $\pi$ ) complexes in the pyridine series (**19**) [75AG634; 76ZN(B)321; 89JCS(CC)995], including chromium(0) complexes prepared from bis(trimethylsilyl)derivatives [91JCS(Pl)501].

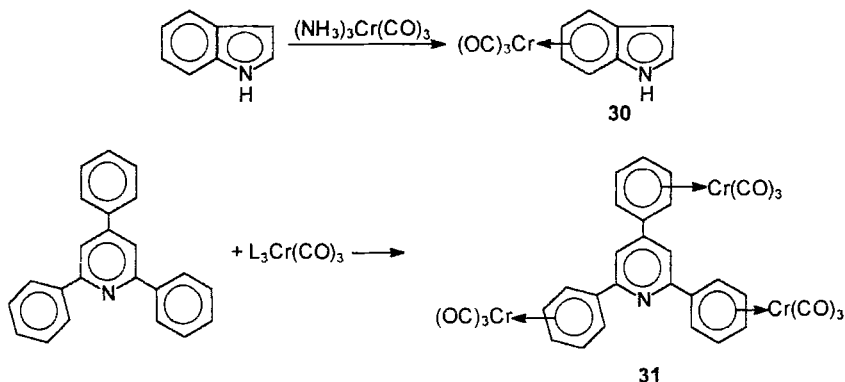


## B. LIGAND EXCHANGE

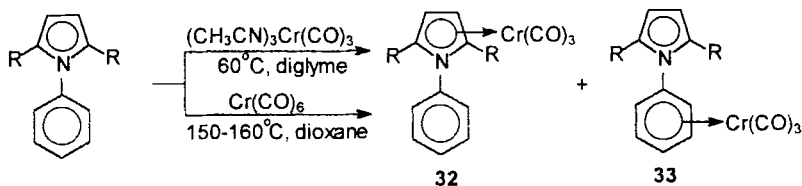
Ligand exchange is applied to the synthesis of  $\pi$ -complexes (**2**, **3**, **6-9**). Acetonitrile, tetrahydrofuran, and pyridine are the typical leaving ligands. UV irradiation is employed in such reactions effectively. Tricarbonylchromium complexes of acetonitrile,  $[(\text{CH}_3\text{CN})_3\text{Cr}(\text{CO})_3]$ , and pyridine,  $[(\text{py})_3\text{Cr}(\text{CO})_3]$ , were starting agents for the preparation of the  $\pi$ -complexes of thiophene (**20**). The tripyridyl complex was used for the synthesis of pyrrole  $\pi$ -complex (**21**). The complexes of tetrahydrofuran with hexacarbonylchromium, -molybdenum, and -tungsten were used to prepare azole derivatives (**22**) (72JOM325, 72ZOB929), and the chromium derivative yields the  $\eta^6$ -2,4,6-trimethylpyridine tricarbonylchromium species (**23**)







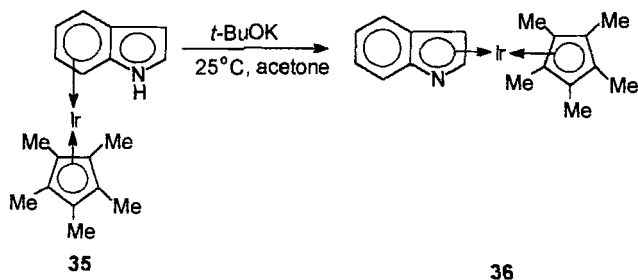
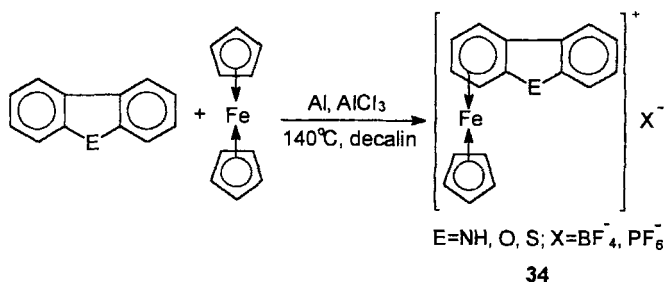
A series of complexes with the  $\pi$ -bonded aromatic and heteroaromatic frameworks **6** and **9** was prepared by ligand exchange. An example is the preparation of the  $\eta^6$ -tricarbonylchromium complex of indole (**30**) (68JOM359). Ligand exchange may lead to complexes **9**. Thus, interaction of 2,4,6-triphenylpyridine with  $\text{L}_3\text{Cr}(\text{CO})_3$  yields the trinuclear  $\pi$ -complex



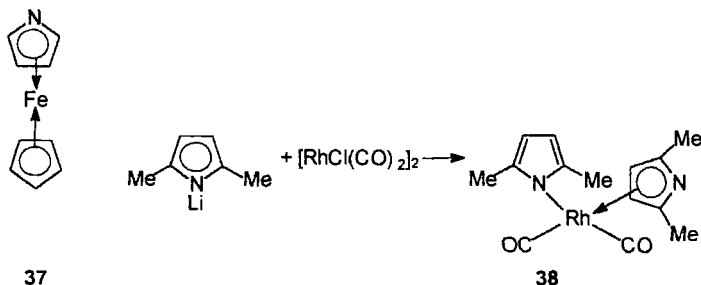
(**31**) (73JOM271). The transformation illustrates the simultaneous formation of complexes **8** and **9** as exemplified by **32** and **33** (71JOM211). Complexes **7** may be obtained by the interaction of benzannulated heterocycles with  $\pi$ -complexes that yield  $\eta^6$ -arene derivatives (**34**). The shift of the metal-containing  $\eta^5$ -pentamethylcyclopentadienyl framework from the arene to hetarene ring is illustrated by the transformation of **35** to **36** (83KGS1155).

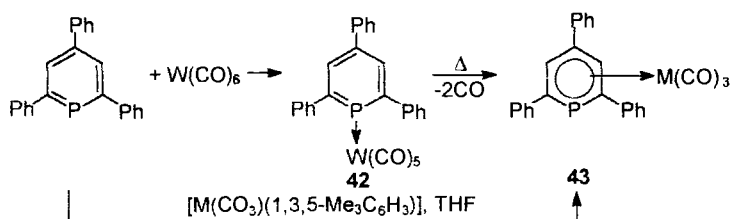
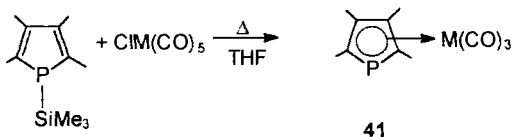
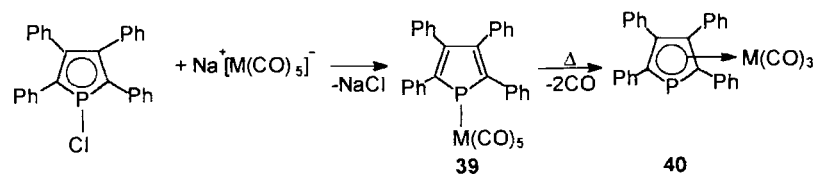
Metal exchange reactions start with the N-alkali metal substituted derivatives of the nitrogen heterocycles. Metal exchange was applied to synthesis of the transition-metal  $\sigma$ -complexes **10** in the pyrazole [80CI(M)323; 84MI6] and tetrazole (69CCR463) series. Interaction of the potassium (lithium) salts with the metal carbonyl halides [e.g.,  $\text{CpFe}(\text{CO})_4\text{I}$ ] in high-boiling solvents yields not only complexes **2**, e.g., **18** (64JOM471), but also the mixed-ligand azaferrocene **37** (64IC796). An unusual transformation affords the  $\pi,\sigma$ -complex **38** [87JOM(319)221; 90POL1503].

Interaction of the P-substituted derivatives of phosphole with anionic



metal carbonyls is used to prepare both  $\sigma$ - (**39**) and  $\pi$ - (**40**) complexes [79JCS(D)814]. The  $\eta^5$ - ( $\pi$ -) complexes of phosphole (**41**) and arsole are prepared by reacting the trimethylsilyl derivatives of heterocycles with halocarbonyl derivatives (82MI1). The  $\sigma \rightarrow \pi$  transformation was used to prepare the  $\eta^1$ - (**42**) and  $\eta^6$ - (**43**) structures in a series of phosphabenzenes. The series **43** was isolated as a result of the ligand exchange starting from the mesitylene complex of tricarbonylmolybdenum or tungsten (73CB2222).



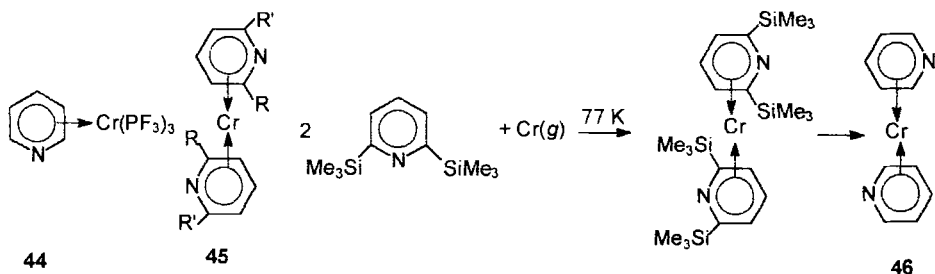


### C. SYNTHESIS OF THE HETARENE COMPLEXES FROM THE ZERO-VALENT METALS

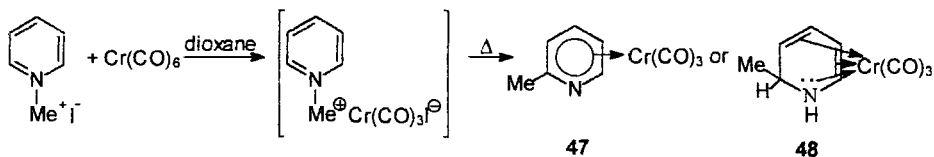
Synthetic methods based on the zero-valent metals include gas-phase [75AG(E)273; 95RCR201; 96MI11; 97MI1, 97MI2] and electrochemical reactions (76ZOB675; 84KK1011; 86MI4).

#### 1. The Gas-Phase Synthesis

In the gas phase, the co-condensation of chromium vapors with azines and subsequent cooling (77 K) led to the first  $\pi$ -complexes of pyridine (**44**, in the presence of  $\text{PF}_3$ ) [75AG(E)273] and (**45**) (76JA1044). The gas-phase synthesis was utilized to prepare the parent bis(pyridine) sandwich species (**46**) (88CB1983). An attempt to prepare the  $\eta^6$ -complex of pyridine was



undertaken as early as in 1959 [59ZN(B)736]. It was concluded that compound **47** had been obtained. However, in reality it was the aminomethylene  $\sigma,\pi$ -complex **48** (67JOM5). The drawback of the gas-phase reactions is the complexity of the apparatus used and the low yield of products, only several percent. Therefore, such reactions cannot be used as a preparative route.



## 2. Electrosynthesis

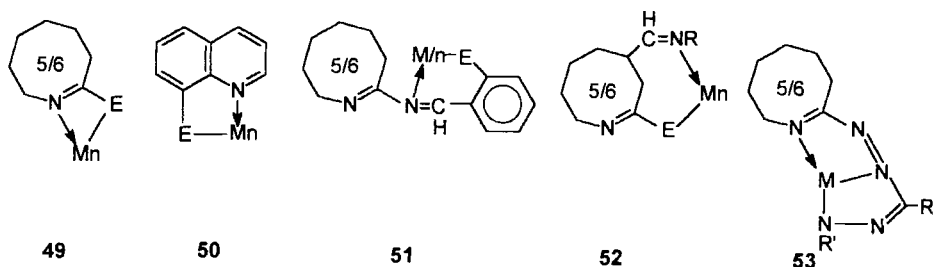
The electrochemical reactions characterized by a high yield of complexes were applied mainly to the synthesis of N-substituted derivatives in the azole series. The electrochemical synthesis is valuable for the preparation of the N-M derivatives of azoles having low-acidity NH groups. It is conducted under mild conditions (room temperature, most often a methanolic medium) using the complex-forming metals as cathodes. They occur with direct and alternating current conditions. Sophisticated apparatus is not required. It is essential to have a reactor (a flask or a beaker) supplied with the electrodes made of the complex-forming metals (anode) and platinum (cathode). Electrosynthesis is widely applied for the preparation of hetarene chelates, e.g., Ni(II) complexes of 2,2'-bipyridine and 1,10-phenanthroline (96ZOB610).

## D. SYNTHESIS OF HETARENE METAL CHELATES

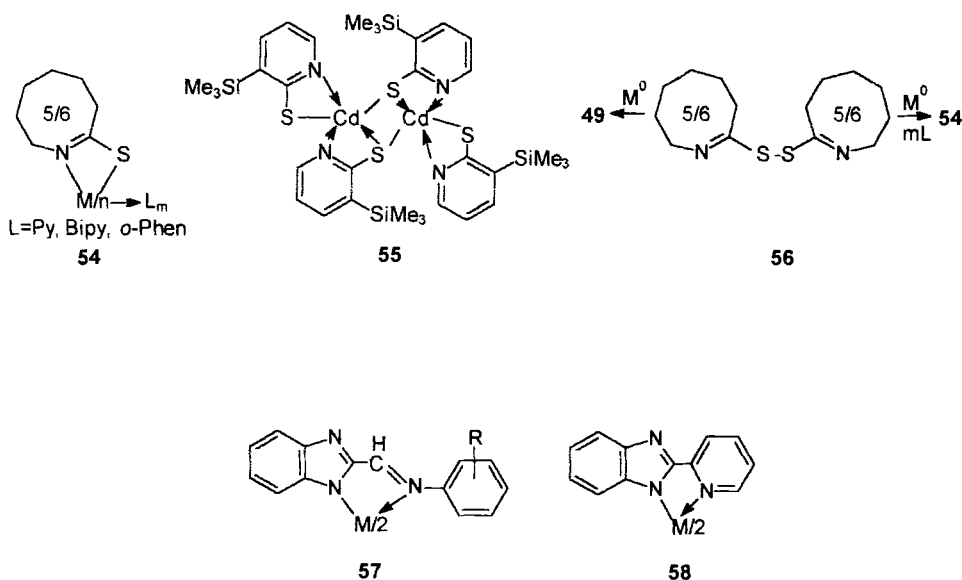
Methods described earlier, excluding the gas-phase synthesis, are applied to the preparation of complexes based on chelate ligands (**12–16**).

The basic method is the direct interaction of **12–16** with metal salts in protic solvents of high polarity. Methanol ensures a high solubility of the ligands and a facile dissociation of the EH groups and metal salts. Transition metal acetates cause favorable conditions (pH ~5.5–6) for the synthesis of metal chelates. Application of nitrates, halides, sulfates often requires higher pH. The nature of reagents and conditions for the complex-formation reactions with the hetaryl chelating ligands has been analyzed in reviews on 2-hydroxy- (mercapto-) nitrogen heterocycles (**49**) (85CCR115;

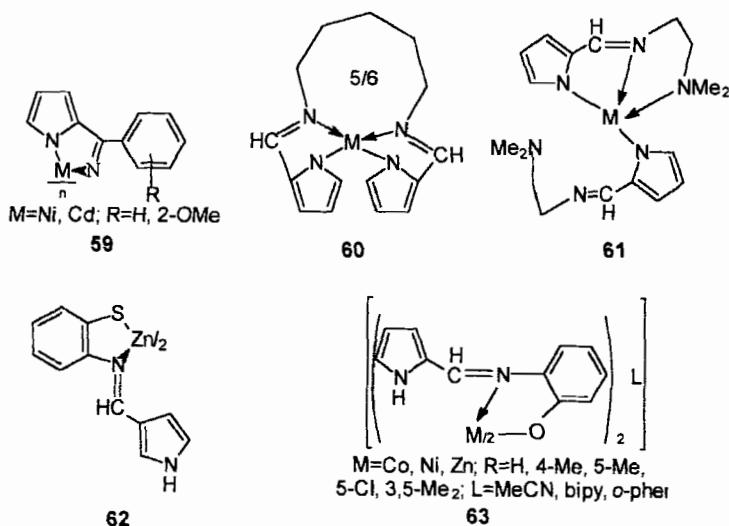
87MI4; 95CCR313), 8-hydroxy(mercapto)quinolines (**50**), azomethines (**51**) and (**52**) (93MI5; 96MI14), and formazanes (**53**) (91KK1011; 96MI12).



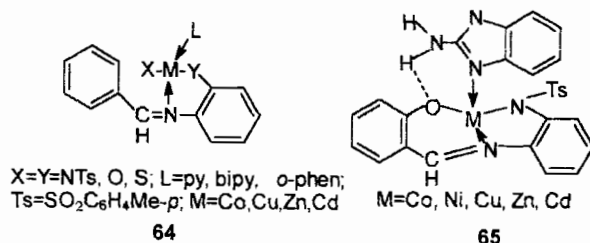
Electrosynthesis is used for the preparation of hetaryl chelates **49**–**53**. Success is achieved in the synthesis of the chelates **49** and adducts with N-bases **54** [90JCS(D)531; 94ICA(221)177, 94POL273]. Electrosynthesis of the chelates from **12** yields not only the monomeric complexes **49** and **54** but also the dimeric products **55** [93ICA(211)47]. Both **49** and **54** can be produced from bis-hetaryldisulfides **56**. Electrolysis enhances the mobility of the NH hydrogen atom of hetarenes as confirmed by the preparation of the chelates **57** and **58**. Pyrrole behaves differently. Using the electrochemical method, both chelates with replacement of the NH hydrogen atom by

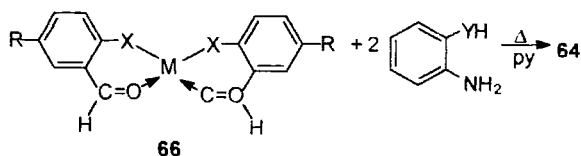


a transition metal, (**59–61**) and complex compounds **62** and **63**, when the pyrrolic fragment does not participate in coordination, were prepared. A series of complexes (**59**) may be obtained chemically (71ZC81; 80UK1234).



Electrosynthesis yielded a series of adducts of the heterocycles with tridentate azomethine ligands, **64** [93ICA(203)67; 94POL1735; 95POL663] and **65** (961ZV2093, 96MI22, 96ZOB147). Electrosynthesis of the adducts **64** and **65** is performed when the azomethine ligands and hetarenes (L) interact with metal plates in acetonitrile at room temperature. The chelates (**64**) may be prepared chemically [92KK974; 93ICA(210)177; 95MI9, 95POL2953, 95ZOB829] from solutions of the ligands and metal acetates in methanol. Because the azomethine ligands are stable, complexes (**64**,  $X = S; Y = NTs, O, S$ ) were prepared as a result of the template reaction of (**66**) and *o*-substituted derivatives of aniline in pyridine medium.





## E. OTHER METHODS OF SYNTHESIS OF HETARENE COMPLEXES

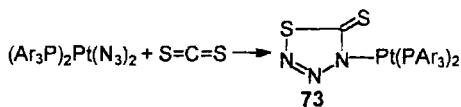
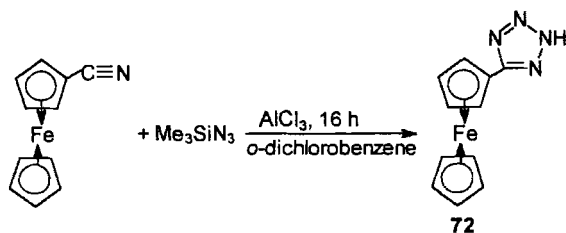
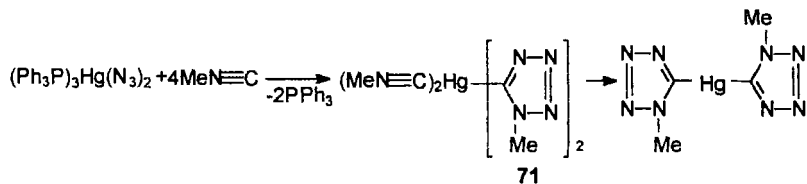
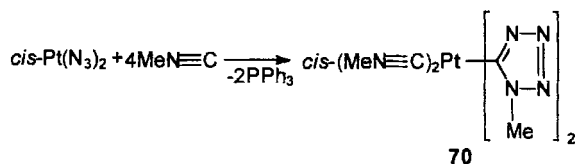
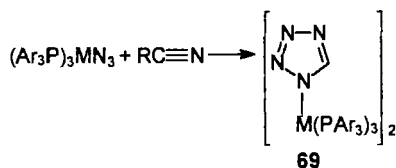
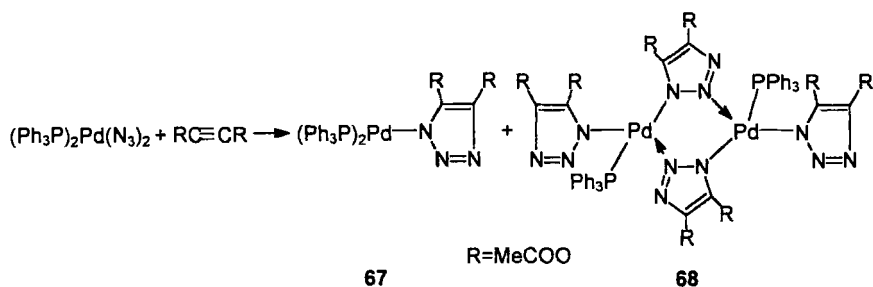
### 1. 1,3-Dipolar Cycloaddition

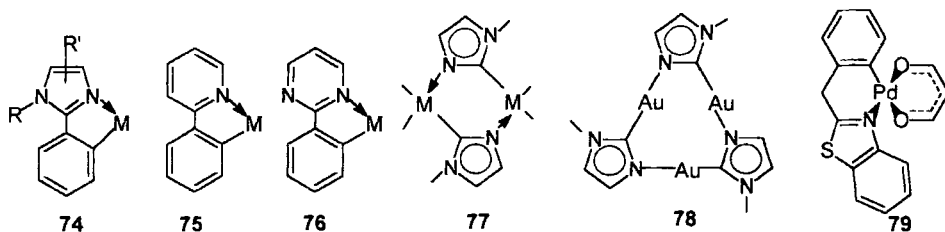
Complexes of the heteroaromatic compounds may be prepared by building up the heterocyclic ligand. The most effective method for the N (**10**, E = N) and C (**11**) derivatives is 1,3-dipolar cycloaddition from the metal azides. The N and C derivatives of triazole (**67**) and (**68**), tetrazole (**69–72**) and other azoles, e.g., **73**, were prepared. The transformations leading to the complexes are summarized later.

### 2. Cyclometallation

A convenient way for the preparation of complexes of heterocycles is cyclometallation [85UK253; 86MI2; 88UK434; 90CRV403; 91TH1; 93CRV861; 95CRV2405, 95MI3; 96IC4883, 96IC4889, 96JOM(522)97]. This reaction often occurs when the hetarene ligands interact with the acetates of platinum group metals, especially palladium. It yields the cyclometallated 2-N,C derivatives of azoles and benzoazoles, e.g., **74** (92JA4230; 93AG432), azines **75**, **76** and others [91MI5; 92MI4; 95IC2334, 95JCS(D)999, 95MI7]. The  $\sigma$ -N,C complexes may be formed as a result of both intra- and intermolecular metal ring formation as exemplified by dimeric (**77**) [93AG(E) 993; 94JOM(465)267] and trimeric (**78**) [89JOM(375)147; 91JOM271; 94JOM(470)275] complexes of imidazole. Another example is the six-membered cyclopalladated complex of 2-benzylbenzothiazole (**79**) (96POL115). A number of mercury-containing cyclometallated products, e.g., of 2-acetylthiophene [87JOM(336)293], 2-phenylpyrrolyl (L) forming a cyclometallated tetramer  $\text{Hg}_4\text{L}_4\text{Cl}_4$  [89JCS(CC)570], 1-phenylpyrazoles, and other ligands (93AJC1323) have been formed. Reaction of 2,9-diphenylphenanthroline with mercury(II) acetate yields the N,C-coordinated species, so that the bridging framework  $\text{LHg}_2\text{Cl}_2\text{L}$  is formed (94IC3656).





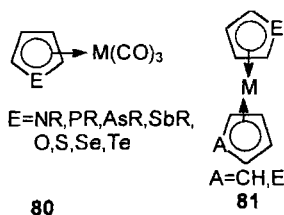


#### IV. Structures of Complex Compounds from Five- and Six-Membered Hetarenes

Donor atoms (E) and aromatic rings form the basis for the ability of heteroaromatic ligands to form complex compounds with localization of the coordination bond via the  $\eta^1$ -E and/or  $\eta^n$ -donor centers ( $n = 5, 6$ ). Competitive coordination of this type (72RCR341) makes it reasonable to subdivide the hetarene ligands into the  $\pi$ -excessive and  $\pi$ -deficient groups (68MI1; 77KGS723; 79KGS1155; 85MI1). The  $\pi$ -excessive are the five-membered heterocycles. They form predominantly the  $\pi$ - ( $\eta^5$ -) complexes. The  $\pi$ -deficient ligands include azines and related phosphorus, arsenic and antimony derivatives. Formation of the  $\sigma$ - ( $\eta^1$ -) coordinated structures is typical. Azoles, although conventionally  $\pi$ -neutral, are practically the  $\sigma$ - ( $\eta^1$ -) ligands. This is unexpected because azoles combine the properties of the  $\pi$ -deficient and  $\pi$ -excessive systems (73KGS99). To elucidate the coordination mode in the hetarene  $\sigma$ - and  $\pi$ -complexes different physical methods are used. However, the most reliable results have been obtained by X-ray structural analysis.

##### A. COMPLEXES OF FIVE-MEMBERED HETEROCYCLES WITH ONE HETEROATOM

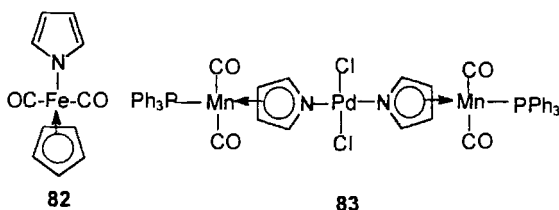
Reviews quoted earlier as well as (96MI20) contain a large number of examples that indicate the prevailing  $\pi$ - ( $\eta^5$ -) complex formation **80** and **81** for five-membered hetarenes. A recent example is the product of the reac-



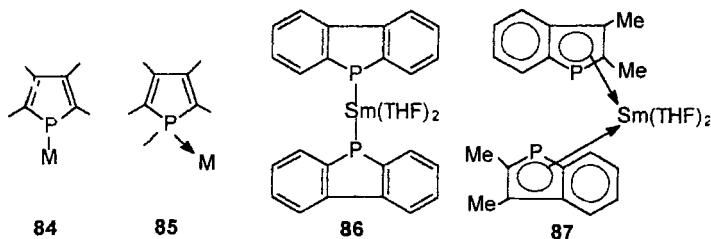
tion of the lithium salt of tetramethylpyrrole with  $\text{TaMe}_3\text{Cl}_2$  (96IC3228). One of the chlorine atoms is replaced and the  $\eta^5$ -complex is formed. The  $\sigma$ - ( $\eta^1$ -) and numerous other coordination modes are less well known and will be considered in detail later.

### 1. Coordination Compounds of Hetarenes with Group V Elements

The  $\sigma$ - ( $\eta^1$ -) complexes are known for pyrroles and phospholes. For pyrroles, both N-metal derivatives (**10**) and organometallic compounds (**82**) and (**83**) are described. A similar situation is observed in pyrrolylimido complexes  $\text{trans}[\text{MX}(\text{NNC}_4\text{H}_4)(\text{dppe})_2]^+$  and  $\text{cis,mer}[\text{WX}_2(\text{NNC}_4\text{H}_4)(\text{PMe}_2\text{Ph})_3]$ , whose reaction ability has been studied comprehensively (95JA12181). A mixed  $\eta^1:\eta^5$  coordination is realized in the binuclear  $\text{Cr}(\text{CO})_5$  complex of azaferrocene (90MI4).



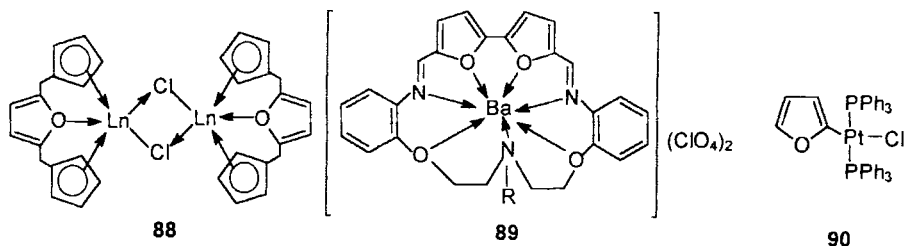
The  $\eta^1$ - (P-) coordinated complexes of phospholes are represented by **84** and **85** (93OM98), **84** being more widely spread. The  $\eta^1$ -coordinated complexes **1** and **10** (E = N, P, As, Sb, Bi) with  $\text{Mn}(\text{CO})_5$  (87NJC585) and dibenzophosphole with samarium (**86**) [94JOM(464)149] serve as examples. Thermal coupling reactions of 1-phenyl-3,4-dimethylphosphole within the coordination sphere of palladium(II) have been studied (96IC1486, 96IC3904). The  $\pi$ - ( $\eta^5$ -) complexes of phospholes **2** and **6** are known as well (96BSF541, 96PS109). Among the latter, **87** is a good illustration. There are examples of  $\eta^1:\eta^5$  coordination, even for sodium methylate [96AG(E)1125] in the complex of the phosphole tetramer. A similar bridging coordination



of the phospholyl ligands is realized in the heterobinuclear zirconium (ytterbium)–ruthenium dihydrides (96OM4178).

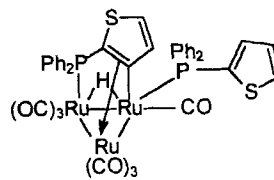
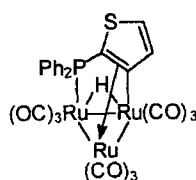
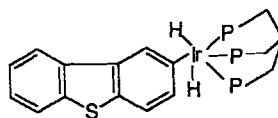
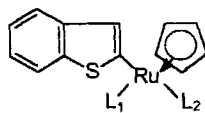
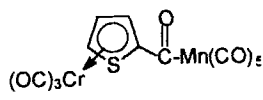
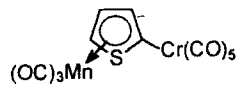
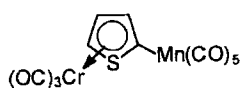
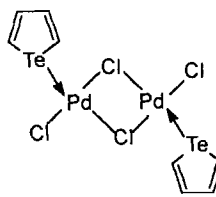
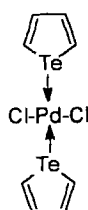
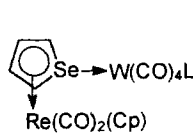
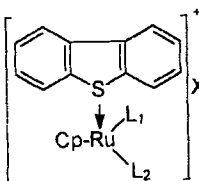
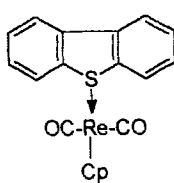
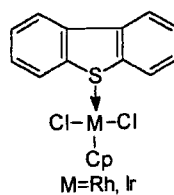
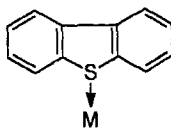
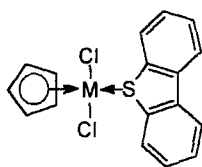
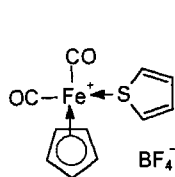
## 2. Coordination Compounds of Heteroarenes with Group VI Elements

The possibility of coordination via the oxygen atom of the furan ring is unclear (96KGS867). Complex **88** [94JCS(D)1599], for which there is no X-ray structural proof, and complex **89**, in which the furan heterocycle is within a macrocyclic ligand, are possible examples [95ICA(231)217]. Stabilization of structures **88** and **89** is perhaps related to chelate and macrocyclic effects (94CCR39; 96MI4). Furan gives rise to organometallic compounds with M–C and M–O frameworks (93OM3800). 2-Furanylplatinum complexes (**90**) are known (95CL1019).



Complexes of thiophene in which the coordination bond is localized at the sulfur atom are represented by a variety of structures, e.g., the ionic complex **91**. The  $\eta^1$ -S coordination is characteristic for the dibenzothiophene complexes (**92–96**) (91IC1417, 91IC5046, 91JA559, 91JA4005, 91OM2438; 93IC1871). The selenium atom of selenophene may also participate in coordination, e.g., **97** (90JA7811). Compounds **98** and **99** (72JOMC87; 82CCR133; 86MI3; 87MI3) represent the  $\eta^1$ -Te-coordinated tellurophene complexes. A similar coordination mode may be observed in the complexes of tellurium heterocycles with chlorides and carbonyl chlorides of mono- and trivalent rhodium (90POL1141). Mixed  $\eta^1$ - (C-) :  $\eta^5$ -complex formation is realized in a series of complexes (**100–102**) [93AG(E)710]. Benzothiophene and dibenzothiophene form the  $\eta^1$ - (C) complexes **103** and **104**, respectively (95OM2342, 95OM4390). Reaction of diphenyl-2-thienylphosphine with  $\text{Ru}_3(\text{CO})_{12}$  follows a nontrivial route leading to a mixture of clusters (**105,106**) (96OM786).

Up to 1994 the majority of publications on five-membered monoheterocycles were on phospholes. Since 1995, thiophene has become the ligand of the year. The organotransition metal chemistry of thiophene has been the subject of a substantial number of reviews on its pure and applied chemical

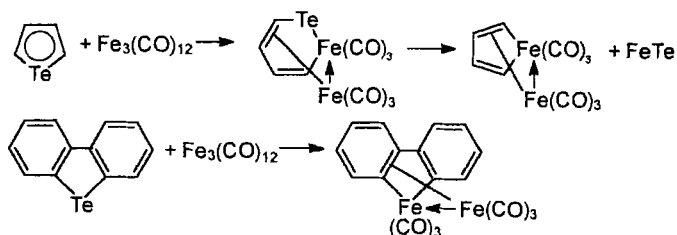


nature. A series of coordination modes and the reaction ability of thiophenes in transition metal complexes compose the first group of reviews (87CCR279; 90S89; 91PIC259; 95BSB265). Catalytic and material chemistry is well documented [88ACR387, 88ACR394, 88CRV183; 91AOC349, 91CI(L)570, 91MI2; 92CRV451, 92CRV711; 94MI2, 94MI6; 96JCS(D)801]. To present the modern state of affairs, especially on such an exciting subject as the reactivity pattern of free and differently coordinated thiophene and some of its derivatives, we would need a review of the same size as this one. Herein we attempt to cover the recent data that show the variety of coordination modes.

The  $\eta^5$ -thiophene complexes  $[(T)Mn(CO)_3]^+$  ( $T$  = thiophene or, more often, 2,5-dimethylthiophene) add nucleophiles  $R$  (from  $LiCuR_2$ ,  $R$  = Me, Ph) via the sulfur atom to yield the  $\eta^4$ -coordinated species. Thus, the sulfur atom is an electrophilic center in the  $\eta^5$ -complexes (96OM325). The reaction of  $Cp^*Ir(\eta^5-T)(BF_4)_2$  with the reducing agent  $Cp_2Co$  yields a mixture of products  $[Cp^*Ir(\eta^4-T)]$ , opened-ring  $Cp^*Ir(C,S-T)$ , and  $Cp^*(\eta^4-T-C_5H_4)$  (96OM1223). The same dication reacts with  $[CH(COOMe)_2]^-$  to give  $Cp^*Ir[\eta^4-T-C(COOMe)_2]$  with an opened-ring thiolate ligand [96JOM(512)149]. With  $(\mu-S)_2Fe(CO)_6^{2-}$ , it gives the Fe-S-coordinated  $Cp^*Ir[\eta^4-TFe_2(CO)_8(\mu-S)_2]$  [96JOM(522)21]. The iridathiabenzene complex  $[Cp^*Ir(C,S-T)]$  reacts with  $(\eta^6-C_6H_3Me_3)Co_4(CO)_9$  to yield an  $\eta^6$ -complex of  $Co_4(CO)_{12}$  (96OM1414). The  $\eta^4$ -complex  $Cp^*Ir(\eta^4-T)$  is presented as two isomers, the one just mentioned and the other mentioned a bit earlier as the opened-ring complex. The reaction with various metal carbonyls or sandwich complexes proceeds differently depending on the nature of the attacking agent. Reaction with  $Ru_3(CO)_{12}$  gives the  $\eta^4 : \eta^1$  heterobimetallic species containing a triangular  $Ru_3$  cluster. A similar situation is observed for the interaction with  $Re_2(CO)_{10}$ , although there is no cluster formation in this case, but a  $Re(CO)_4-Re(CO)_5$  moiety  $\eta^1$ -bound to the sulfur atom. The other product is the opened-ring structure, and the latter is the predominant result of the reaction with  $Mn_2(CO)_{10}$ .  $[(\eta^6-C_6H_6)RuCl_2]_2$  again forms the mixed  $\eta^4 : \eta^1$  coordinated species (96OM2727). Photochemical reaction of thiophene or 2,5-dimethylthiophene with  $Ru(PMe_3)_2(CO)Cl$  yields unique products of C-H insertion, e.g., *trans*- $Rh(PMe_3)_2(CO)Cl(2,5\text{-diethyl-}1,3\text{-thienyl})H$  (96OM872). Thiophene and benzo[*b*]thiophene react with  $[(triphos)IrH]$  to yield a mixture of the C-H and C-S insertion products (triphos =  $MeC(CH_3)PPh_2$ ) [95JOM(504)27]. The other ring-insertion reaction is the interaction of benzo[*b*]thiophene with  $Pt(PEt_3)_3$ , leading to the addition product containing the platinum-sulfur bond in the metallocycle (96MI13). Similarly, the  $\eta^6$ -coordinated complexes of benzo[*b*]thiophene (BT) possess various reactivity patterns. Thus,  $Cr(CO)_3(\eta^6-BT)$  reacts with  $Cp(CO)_2Re(THF)$  to yield

$\text{Cp}(\text{CO})_2\text{Re}(\eta^2: \eta^6\text{-}\mu_2\text{-BT})\text{Cr}(\text{CO})_3$ , in which chromium is coordinated via the benzene ring and Re is bound to the  $\text{C}_2=\text{C}_3$  bond of the thiophene ring [compare with  $\text{Cp}(\text{CO})_2\text{Re}(\text{BT})$  in which there is an isomerism of the  $\eta^2\text{-C}_2=\text{C}_3$  and  $\eta^1\text{-S}$ -coordinated species] [95ICA(240)393]. Reaction of  $[\text{Mn}(\text{CO})_3(\eta^6\text{-BT})]\text{BF}_4$  occurs via the insertion of the manganese atom into the C-S bond of the heterocycle [96AG(E)212].

The nature of the complexes of tellurophene and its benzo analogs depends on the type of metal carbonyl. Thus, interaction of tellurophene with  $(\text{MeCN})_3\text{Cr}(\text{CO})_3$  yields the  $\eta^5$ -complex [2; E = Te; M =  $\text{Cr}(\text{CO})_3$ ], whereas the reaction with  $\text{Fe}_3(\text{CO})_{12}$  is a complicated transformation [96JCS(D) 1545]. A similar reaction is observed for dibenzotellurophene.



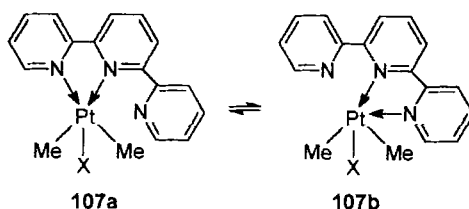
## B. COMPLEX COMPOUNDS OF AZINES AND THEIR PHOSPHORUS- AND ARSENIC-CONTAINING ANALOGS

Modern studies reject the idea that pyridine is exclusively an  $\eta^1$ - (N) donor. Indeed, azines and their P and As analogs form the  $\pi$ - ( $\eta^6$ -) complexes as well.

### 1. $\eta^1$ - ( $\sigma$ -) Complexes

The most widespread and well-known coordination mode for the azines is  $\eta^1$ - (N-) metal bonding (63PMH161; 82MI2; 85HC161; 92MI3). Reference data on the X-ray structural analysis of the complexes of pyridine  $[\text{Py}_m \cdot \text{MX}_n]$  are generalized in Elsenbroich *et al.* (92AG1388). In the same publication evidence for the existence of the complex of pyridine with zero-valent nickel in solution,  $[\text{NiPy}_4]$  is provided. The complexes of pyridine with  $\text{BH}_2\text{CN}$  [90ICA(172)35], copper acetate (93KK64), and the ruthenium cyclopentadienyl framework (91OM1209), and of 4-styrylpyridine with iron thiocyanate (94IC2273), as well as in the binuclear complexes

$[\text{Rh}_2(\text{CH}_3\text{COO})_2\text{Py}_4]\text{CF}_3\text{SO}_3$  and  $[\text{Rh}_2(\text{CH}_3\text{COO})_2\text{Py}_6](\text{CF}_3\text{SO}_3)_2$  (88MI3) are described. The pyridine–lithium complex  $\text{LiPy}_3(\text{CHCl}_2)$  is of interest (96AG1639). The reaction of  $[\text{Os}_3(\text{CO})_{10}(\mu\text{-H})_2]$  with *trans*- $[\text{Pd}(\text{py})_2\text{Cl}_2]$  gives  $[\text{Os}_4\text{Pd}(\text{CO})_{11}(\mu\text{-H})_3(\mu\text{-Cl})_3(\text{py})]$  with pyridine coordinated to a singular osmium (not palladium) atom [95JCS(D)3987]. The pyridyl–bipyridyl complex of platinum (**107**) has the structure **107a** in the solid state and an equilibrium of linkage isomers **107a** and **107b** in solution [93JCS(D)291].

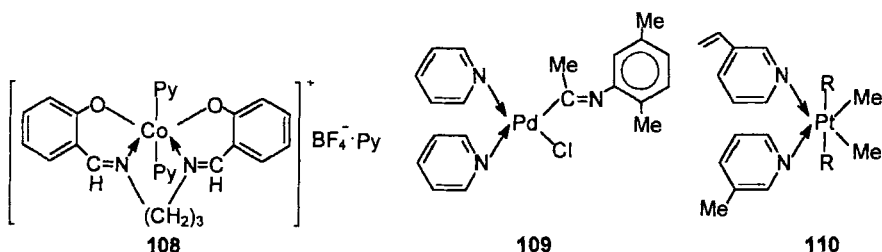


Pyridine and other azines often serve as the N-coordinated ligands in the adducts of chelates of the mercapto derivatives of azines (**54**) and tridentate azomethines (**64**). Publications [92G229, 92ICA(194)1; 94ICA(216)215, 94ICA(217)194; 95JOM(505)135; 96IC2715] are devoted to the study of the adducts used for modeling vitamin B<sub>12</sub> and the corrole complex of iron (94AG771). A similar coordination is observed in **108** [96AX(C)1146]. The  $\eta^1$ - ( $\sigma$ -) coordination is characteristic for the cobalt(0) bis(pyridyl) complex prepared by a gas-phase synthesis (81IC3629) and for azines containing two nitrogen atoms in the heteroring, e.g., pyrazine [90IC3321; 94ICA(217)39]. A 1,2-metallotropic shift in trimethylplatinum(IV) complexes of pyridazine *fac*- $[\text{PtMe}_3(\text{L-L})(\text{pydz})]\text{BF}_4$ , where L-L is a variety of neutral bidentate chelate ligands, has been studied as a function of the nature of L-L [95JCS(D)3165].

A popular group of ligands is based on 2,2'-bipyridine and 1,10-phenanthroline (87CRV711). The spectrochemical studies of rhenium(I),  $\alpha,\alpha'$ -diimine complexes such as  $[\text{Re}(\text{bipy})(\text{CO})_3\text{Cl}]$  and a variety of related complexes is ongoing [95JC(D)3677; 96JA3057, 96JCS(D)3065, 96MI19, 96OM236]. The same is true for the radical-anionic  $\text{M}(\text{CO})_4$  complexes of the derivatives of 1,10-phenanthroline (96IC1295). The molybdenum(VI) dioxodialkyl complexes of composition  $\text{MoO}_2\text{R}_2(\text{bipy})$  ( $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$  and *p*- $\text{MeC}_6\text{H}_4\text{CH}_2$ ) are known [95TMC(L)426]. A phenylating agent on  $[\text{Pd}(\text{dmphen})(\text{olefin})]$  substrates (dmphen = 2,9-dimethyl-1,10-phenanthroline) is dichlorodiphenyllead(IV), which finally affords  $[\text{PdPhCl}(\text{diolefin})]$  as a parent in a new organometallic series (95OM5410). The compounds  $\text{PbMe}_2\text{Cl}_2$  and  $\text{PbPh}_2\text{Cl}_2$  oxidatively add to the three-coordinate chelate complexes of platinum(0) as in  $[\text{Pt}(\text{phen})(\text{olefin})]$  (phen = 2,9-

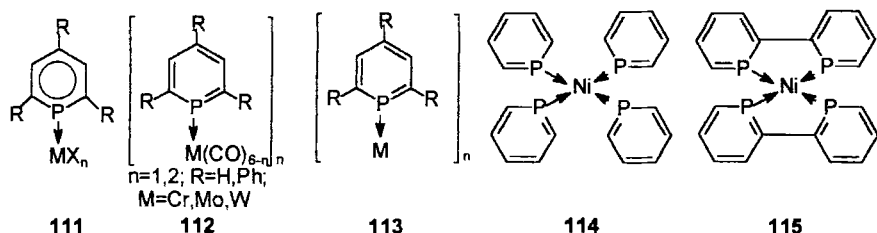


dimethyl-1,10-phenanthroline) to yield  $[\text{Pt}(\text{Cl})(\text{PbR}_2\text{Cl})(\text{phen})(\text{olefin})]$ , in which the moiety  $\text{Pt}(\text{II})\text{-PbR}_2\text{Cl}$  is stabilized (95OM4213). In the same series of heterobinuclear complexes, the cationic five-coordinate platinum(II) derivatives with alkylmercury fragments are known,  $[\text{Pt}(\text{HgR})(\text{H}_2\text{O})(\text{dmphen})(\text{Z-R}'\text{O}_2\text{CCH}=\text{CHCO}_2\text{R}')](\text{BF}_4)$  ( $\text{dmphen}$  = 2,9-dimethyl-1,10-phenanthroline;  $\text{R}, \text{R}' = \text{Me}, t\text{-Bu}$ ) [95JOM(503)251]. An interesting ligand is based on the phosphorus analog of 2,2'-bipyridine (95BSF910; 96CB263). A good deal of research is devoted to the study of the reactivity of chelates, e.g.,  $[\text{M}(\eta^4\text{-C}_5\text{H}_4\text{O})(\text{CO})_2(\text{bipy})\text{Br}]\text{PF}_6$  ( $\text{M} = \text{Mo}, \text{W}$ ) (96OM2954). As an illustration, cyanide insertion into the species  $\text{MePd}(\text{bipy})\text{Cl}$  and  $\text{MePd}(\text{phen})\text{Cl}$ , yielding **109**, may be mentioned [95JCS(CC)223]. Reactions of the related palladium complexes can be found in [96JOM(510)219, 96JOM(513)98]. The complex  $[\text{PtMe}_2(t\text{-Bu}_2\text{bpy})]$  oxidatively adds  $(\text{R}_2\text{SnS})_3$  to give the platinum(IV) product (96OM1749); **110** is mentioned in Achar



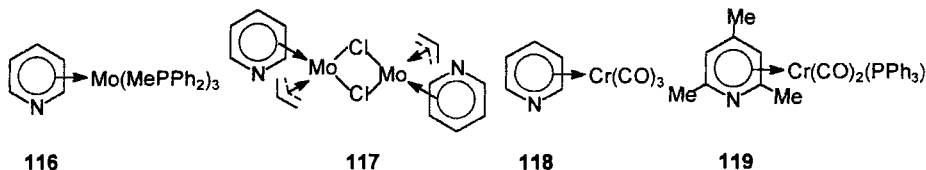
*et al.* (96POL2363). Complexes  $[\text{RhCl}_2(\text{C}_4\text{H}_7)(\text{phen})]$  are remarkable for their catalytic properties [96TMC(L)305]. Pyrazine reacts with  $\text{OsO}_2(\text{mesityl})_2$  to yield the dimer  $[\text{OsO}_2(\text{mesityl})_2]_2(\mu\text{-pyz})$ , whereas 4,4'-bipyridyl and *trans*-1,2-bis(4-pyridyl)ethylene give rise to the oligomers, e.g.,  $[\text{OsO}_2(\text{mesityl})_2(\mu\text{-4,4'-bpy})]_4$  (96OM1497). 5,6-Diphenyl-3-(2-pyridyl)-1,2,4-triazine or 3,5,6-tri(2-pyridyl)-1,2,4-triazine in  $[\text{ReCl}(\text{CO})_3\text{L}]$  behave as bidentate species coordinating via a pyridyl nitrogen and one of the triazine nitrogens (96POL203).

The  $\sigma$ - ( $\eta^1$ -) complexes are known for a series of phosphorus- and arsenic-containing analogs of pyridine—phosphabenzene and arsabenzene (**111** and **112**) (90MI1). Complexes **113** were synthesized and structurally characterized [93JOM157, 93ZN(B)1581; 94JA6217]. The reaction of  $[\text{Ni}(\text{cod})_2]$  with phosphabenzene leads to complex **114**. 2-Iodophosphabenzene forms pentacarbonyltungsten species (96OM794). They are also able to form the 2-organozinc derivatives that in turn form the  $\eta^1$ -bound  $\text{W}(\text{CO})_5$  complexes (96OM802). The  $\eta^1$ - (P) bond is formed in the complexes of nickel with the phosphorus analog of 2,2'-bipyridine (**115**) (95IC11).

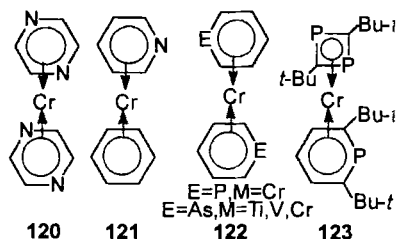


## 2. $\eta^6$ - ( $\pi$ -) Complexes

After the completion of the X-ray structural analysis, no doubts remained about the structure of complexes **2**, **44**, and **45**. Thus, the structure **44** was established for the complexes **116** [83JCS(CC)909], **117** (93JOM125), **118**, and **119** (95ZOB1251). The photochemical reactions of  $(\eta^6\text{-}2,6\text{-R}_2\text{py})\text{Cr}(\text{CO})_3$  ( $R = \text{H, Me, SiMe}_3$ ) were studied in detail (96OM3679). The  $\eta^6$ -complexes



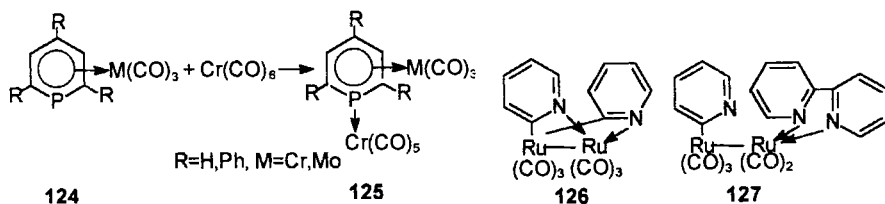
**45** (76IC2735), **120**, and **121** have the sandwich structure. The latter is characteristic for bis(phosphabenzene)- [91AG(E)547; 93OM3373; 96PS173; 97JCS(CC)481] and bis(arsabenzene)chromium (**122**) [86AG(E)571; 93TH1] as well as for the mixed-ligand compound **123** (95AG251). Molybdenum sandwiches of 2,6-lutidine [96JOM(513)247] are known.



## 3. Other Coordination Modes

In the metal-carbonyl complexes (**124**) the phosphorus atom retains its donor properties, which gives rise to the  $\eta^1 : \eta^6$  bonded complexes (**125**).

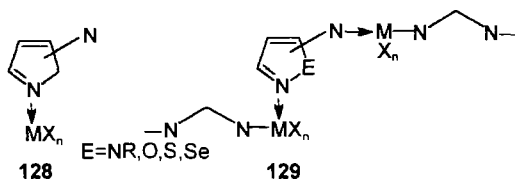
The metal(II) alkyls metal(2-pyridino)bis(trimethylsilylmethyl) or 2-pyridino (trimethylsilyl)methyl ( $M = \text{Cr, Mn, Fe or Co}$ ) are derived from the anions of bis(trimethylsilyl) methylpyridine and 2-trimethylsilylmethylpyridine (HL). They have the composition  $ML_2$  and are characterized by a square-planar ( $M = \text{Cr, Co}$ ) or a distorted octahedral (Fe) geometry (96POL135). The  $\eta^2$ -(N,C) coordination of pyridine is realized in ( $\eta^2$ -(N,C)-2,4,6- $\text{NC}_5(t\text{-Bu})_3\text{H}_2$ )Ta(OAr) $_2$ Cl complexes subjected to a series of further reactions (95JA10678, 95OM5588). An  $\eta^2$ -pyridyl moiety bound to zirconium is known (95OM5478). Unusual coordination of pyridine is manifested in the reaction of 2,3-dichloropyridine with  $\text{NiCl}_2(\text{PPh}_3)_2$  in the presence of zinc when the C,N-bridged dimer  $[\text{NiCl}(\mu\text{-3-C}_5\text{N}_3\text{N-2})(\text{PPh}_3)]_2$  is formed (95POL2637). Among the  $\sigma$ -N,C-metal-containing derivatives of azines, complexes **126** and **127** may be noted (92JOMC36). The other illus-



tration is  $\text{Ru}_3(\mu\text{-H})(\mu\text{-C,N-C}_5\text{H}_4\text{N})(\text{CO})_{10}$  (96MI9) and similar bridges [96JOM(513)202]. An unusual coordination is observed in a triangular anionic cluster  $[\text{Re}_3(\mu\text{-H})_3(\text{CO})_{10}(\mu\text{-NC}_5\text{H}_4)]^-$  in which pyridine is ortho metallated [95JOM(504)15]. The ligand 2-phenylazopyridine reacts with  $[\text{Os}_3(\text{CO})_{10}(\text{MeCN})_2]$  to yield  $[\text{Os}_3(\text{CO})_{10}(\text{NC}_5\text{H}_4\text{N}=\text{NPh})]$  as two isomers, and  $[\text{Os}_3(\text{CO})_{10}(\mu\text{-H})(\text{N-C}_5\text{H}_3\text{-N}=\text{N}(\text{O})\text{Ph})]$ . The pyridine ligand is a six-electron donor in the first of the clusters, whereas it is oxidized and bonded in a ortho-metallated mode in the second [95ICA(238)193]. The  $\mu$ (N,C)-bridging coordination mode is described in the anthracene-containing supramolecular pyridine complexes of osmium clusters [96JCS(D)1853].

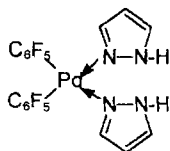
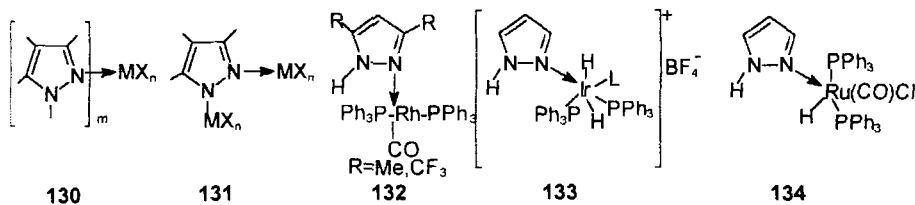
### C. COORDINATION COMPOUNDS OF AZOLES

Azoles are different from the fundamental five-membered heterocycles and azines. They form mainly complexes with coordination via the pyridinic N atom (**1**). Azoles may be monodentate (**128**) or bridging (**129**) ligands. Because only the  $\sigma$ -(N) coordination has so far been proven structurally, it is possible to subdivide the azole complexes according to the type of the endocyclic heteroatoms.



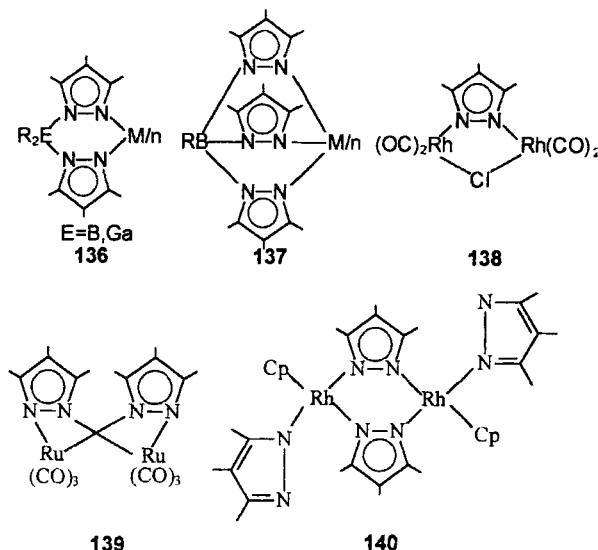
### 1. Complexes of Azoles with Two and More Nitrogen Atoms

The  $\sigma$ - ( $\text{N}, \eta^1$ -) bonding is observed in pyrazole complexes **130** [95ZSK157; 96AX(C)56] and **131** [91JCOC201; 92JCS(D)223, 92JCS(D)2389; 94JCS(D)159]. Structures were proven for  $[\text{Ni}(\text{HPz})_6](\text{NO}_3)_2$  [70AX(B)521] and  $[\text{Ni}(\text{HPz})_4\text{Cl}_2]$  (67AX135; 69RTC1451),  $[\text{Cu}(3,5\text{-Me}_2\text{HPz})_4 \cdot \text{H}_2\text{O}](\text{ClO}_4)_2$  (86ZSK110),  $[\text{Cu}(3,5\text{-Me}_2\text{HPz})_4 \cdot \text{H}_2\text{O}](\text{NO}_3)_2$  (95ZSK157), and  $[\text{Mn}(\text{HPz})_4]\text{Cl}_2$  [88AX(C)1564]. The organometallic  $\eta^1$ -(N) derivatives of pyrazole are known as well. The complexes of rhodium (**132**), iridium (**133**) [94JOM(467)151], ruthenium (**134**) [87JCS(D)183], and palladium (**135**) (91IC2605) can be listed as an illustration.



The range of complexes with the bridging pyrazolate includes **17**, **136**, **137**, and **138**. In two complexes of cadmium the coordination modes **136** and **137** are realized simultaneously [74JCS(D)503; 75CJC2930, 75JCS(D)749; 79CJC2520; 84BSF46; 87IC2310; 95IC4996; 96JOM(511)115]. Com-

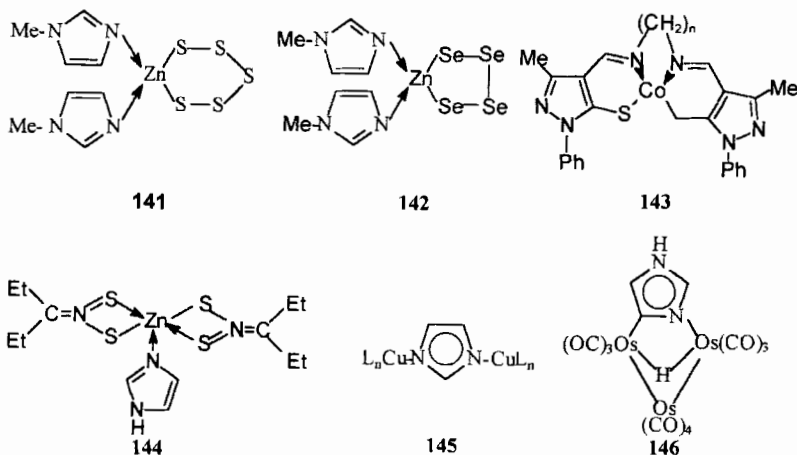
plexes **136** and **137** are considered elsewhere. The bridging pyrazole complexes **138** (85CJC699), **139** [89JOM(379)151], **140** [85ICA(97)19], and others [96ICA(243)47, 96JCS(D)2877, 96OM3785, 96OM4423] are also



known. In the binuclear rhodium complex (**140**), the pyrazole ligand fulfills mono- and bidentate functions simultaneously. A similar situation is achieved in the mixed  $\eta^1 : \mu$  pyrazolyl complexes  $[\text{Ru}_2(\mu\text{-pz})_2(\text{CO})_4(\text{HPz})_2]$  and other species (96OM2979). In the indazole complex of copper chloride  $\text{L}_2\text{CuCl}_2$  the  $\eta^1$ - (N) bonding of the indazole framework is realized (89POL1345). Species  $[\text{M}_2(\mu\text{-Cl})(\mu\text{-pz})(\text{cod})_2]$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) react with  $\text{LiPPh}_2$  to yield the heterobridged  $[\text{M}_2(\mu\text{-pz})(\mu\text{-PPh}_2)(\text{cod})_2]$  [96JOM(509)89].

The complexes of imidazole are represented by **128** with coordination via the pyridinic N atom [84AX(C)768; 90AX(C)1773, 90IC1043, 90JA6385; 91AX(C)1392, 91ICA(190)11, 91MI7; 93AX(C)1298, 93MI7; 94ICA(215)73, 94IJC354, 94JCS(D)361; 96JOM(518)201, 96ZSK176] and by **129** with bidentate metal bonding with both nitrogen atoms. It possible to prepare complexes of compositions  $\text{MX}_n \cdot \text{L}_m$  where  $m = 1, 2, 4, 6$ . The composition  $\text{MX}_n \cdot \text{L}_1$  is typical for the complex  $\text{Mn}(\text{ImH})\text{Cl}_2$ , and  $\text{MX}_n \cdot \text{L}_2$  is realized in  $\text{Co}(\text{ImH})_2\text{Cl}_2$  (72ACS3995),  $\text{Co}(\text{ImH})_2\text{CO}_3 \cdot \text{H}_2\text{O}$  [70JCS(A)2558], and  $\text{Zn}(\text{ImH})_2\text{Cl}_2$  (66AX901),  $\text{MX}_n \cdot \text{L}_4$  in  $\text{Ni}(\text{ImH})_4\text{X}_2$  ( $\text{X} = \text{Cl}, \text{Br}$ ), and  $\text{MX}_n \cdot \text{L}_6$  in  $\text{Ni}(\text{ImH})_6(\text{NO}_3)_2$  [69AX(B)842]. Imidazole forms mainly the complexes  $\text{MX}_n \cdot \text{L}_2$ , e.g.,  $\text{Cu}^{\text{I}}(1\text{-MeIm})_2\text{BF}_4$ ,  $\text{Cu}^{\text{II}}(\text{ImH})_2\text{Ac}_2$ ,  $\text{Cu}^{\text{II}}(2\text{-$

$\text{ClImH})_2\text{Cl}_2$ ,  $\text{Cu}^{\text{II}}(2\text{-ClImH})_2\text{Br}_2$ ,  $\text{ZnS}_6(1\text{-MeIm})_2$ , and  $\text{ZnSe}_4(1\text{-MeIm})_2$ . However, imidazole and derivatives (1-Me-, 1-Et-, 4-Me-, 4,5-Ph<sub>2</sub>-) also form the complexes  $\text{TeX}_3 \cdot \text{L}_5$  ( $\text{X} = \text{Cl}, \text{Br}$ ). The preparation of the monomeric complex  $\text{CuAc}_2(\text{ImH})_2$  is unexpected because the N bases form the dimers  $[(\text{CuAc}_2)_2\text{L}_2]$  (84CCR1). The structures of **141** and **142** are of interest, as is that of the adducts of the metal chelates with imidazole **143** and **144**. Complexes with the bridging imidazolate framework may be represented by **145**. In the di- and trinuclear complexes of imidazole the ligand fulfills the C,N bridging function as exemplified by osmium dimers **146**

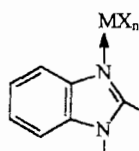
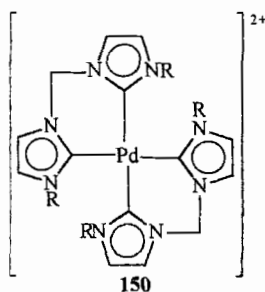
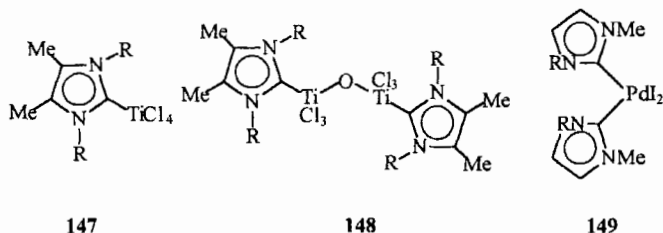


(82IC634; 83JOM349). 2,2'-Biimidazole ( $\text{H}_2\text{L}$ ) reacts with  $\text{Os}_6\text{H}_3(\text{P}^i\text{Pr}_3)_2$  to yield  $\text{OsH}_3(\text{HL})(\text{P}^i\text{Pr}_3)_2$ . The latter further reacts with  $[\text{M}(\mu\text{-OMe})(\text{cod})]_2$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) to afford the heterobimetallic species  $(\text{P}^i\text{Pr}_3)_3\text{H}_3\text{Os}(\mu\text{-L})\text{M}(\text{cod})$  (96IC7811).

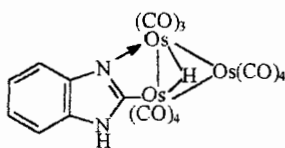
Complexes of imidazolium derivatives in which both nitrogen atoms bear a substituent are famous because they form carbenes [95JOM(498)1], among them the titanium (**147** and **148**) [95ICA(238)179] and palladium (**149**) [95AG(E)2371] carbenes. Another illustration is a series of bis(1-methylimidazolyl)aurate compounds [96JOM(511)177]. The carbene **150** deserves special mention [94ZN(B)494; 95JOM(490)149; 96AG333].

Reactions of pyrazole, imidazole, benzimidazole, and their anions with manganese and iron carbonyls may occur via two possible routes, nucleophilic substitution of a carbonyl ligand and a redox pathway [71DOK112; 81JOMC11, 81JOMC13, 81JOMC41, 81ZN(B)400; 84POL707].

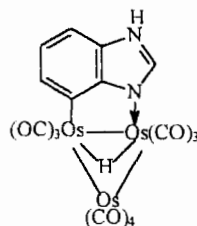
Benzimidazole is characterized by the  $\eta^1$ -(N) metal bonding (**151**) via the pyridinic nitrogen atom [92IJC(A)463; 93IC4256]. However complexes



151



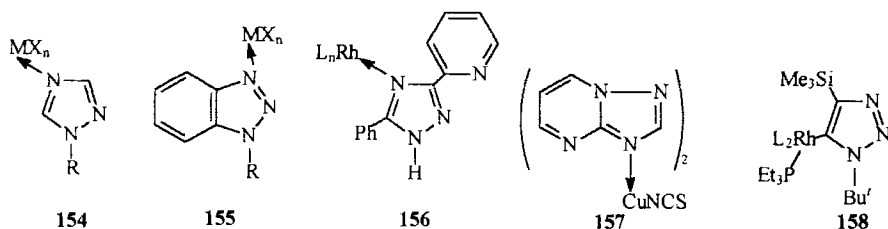
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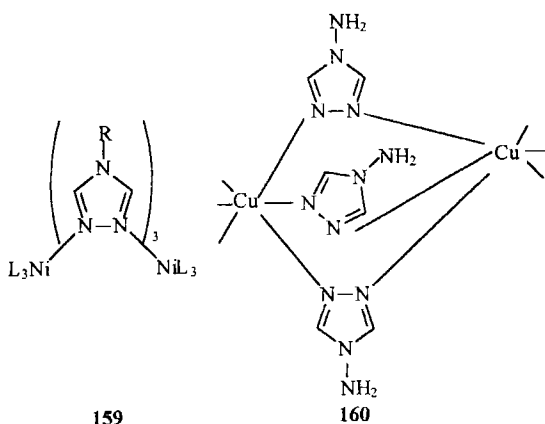
153

are known in which benzimidazole fulfills the C,N bridging function, (**152**) and (**153**) (82IC634).

The complex compounds of triazole and aryl-annulated analogs are represented by 1,2,4-triazole (**154**) and benzo-1,2,3-triazole (**155**) species [78IC3026; 81ACSA(A)733, 81ZN(B)809; 84IC1404; 87MI7; 91IC4038; 93KK566; 94POL1593]. Rhodium is coordinated via the N-4 atom of the hetarene ligand in the complex of 3-pyridyl-5-phenyl-1,2,4-triazole (**156**). The  $\sigma$ - ( $\eta^1$ -) coordination via the N-3 atom similar to that in **155** occurs in the nickel complexes of 1-methylbenzotriazole. The N-1 atom of the pyridine type participates in coordination in the complex of 5(6)-methyl[1,2,4]triazolo[1,5-a]pyrimidine (**157**) (89POL2313). An exception is the product of the reaction of (trimethylsilyl)diazomethyl lithium with  $\text{RhCl}(\text{PR}_3)_3$  ( $\text{R} = \text{Me, Et}$ ) or  $\text{RhCl}(\text{CO})(\text{PEt}_3)_2$  (**158**) (96OM1166). 1,2,4-

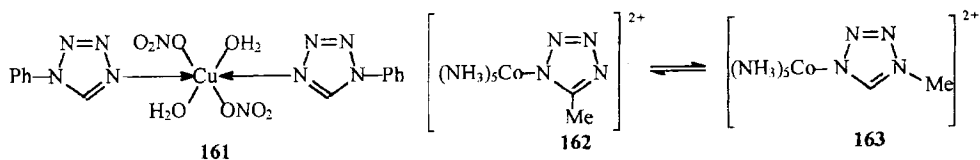


Triazole may act as a bridging ligand, and the N-1 and N-2 atoms may participate in coordination, e.g., **159** and **160**.



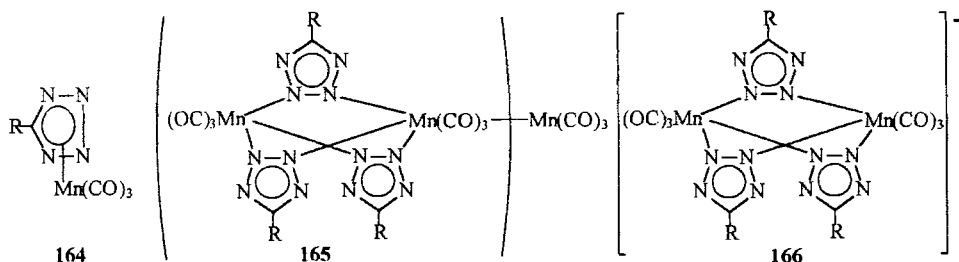
Tetrazole differs by its acidic H atom and predominantly N-metal-substituted derivatives of the type (10). However, for the N-substituted tetrazoles molecular adducts are often formed [71IC661; 88AX(C)367; 89IC2262; 94POL2929] in which the metal is bonded to the N-4 atom. This coordination mode is realized in the *trans*-octahedral complex of 1-phenyl-tetrazole (**161**). Linkage isomerism (72TH1; 80KK1779), involves the cations of the 5-methyltetrazole complexes of penta(ammino)cobalt(III) (**162** and **163**) (91IC3707; 93IC2394; 94IC1921).

The tetrazolate anion is isoelectronic with the aromatic cyclopentadienyl ring and is a potential source of  $\eta^5$ -coordination that can be enhanced by





introducing the electron-withdrawing substituents  $F_2NCF_2$  and  $CF_3$ . In solution the 5-perfluoroalkyl-substituted tetrazoles react with  $Mn(CO)_5Br$  to yield **164** (89IC893) containing the  $\eta^5$ -coordinated tetrazolate ligand. However, when the solvent is removed, the bridging coordination mode **165** is realized. Complex **165** ( $R = CF_3$ ) reacts with  $[Na(digly)_2]^+ Br^-$  to afford **166**, the only structure confirmed by X-ray analysis. Earlier attempts to assign the  $\eta^5$ -structure to the complexes are known. However, in the absence of the X-ray data the structure is insecure.



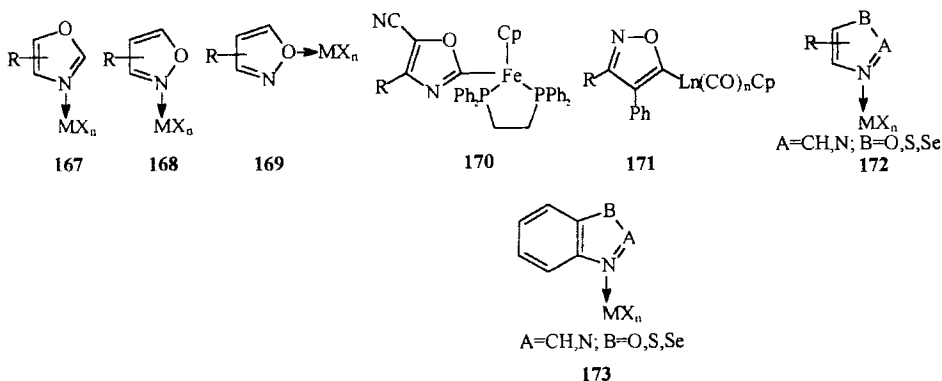
The possibility of using pentazole as a ligand is discussed in literature based on quantum-chemical or other theoretical reasoning. Thus, pentazole, pentazolate anion, or azidopentazole were identified as aromatic species (96IC7124).

In contrast to azoles, their phosphorus analogs tend to form  $\eta^5$ -complexes or the species with a mixed coordination mode (88CRV1327). Thus, the  $\eta^1 : \eta^5$ -species for the phosphorus analog of pyrazole is described (96ZAAC543). The ruthenium sandwich containing the mixed phosphorus, antimony analog of pyrazole belongs to the series of exotic products [96JCS(CC)1591]. The  $P_5$  ligand forms sandwiches and triple-deckers (95CB71, 95MI6; 96PS133, 96ZAAC1478).

## 2. Complexes of Azoles with Endocyclic Atoms—Group VI Elements

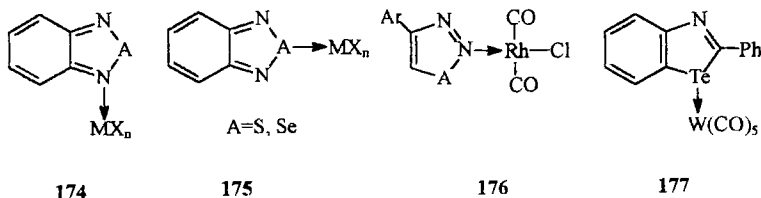
In oxazole (**167**) (95MI5) and isoxazole (**168**) [88ZN(B)328] N-M coordination prevails. The possibility of O coordination (**169**) is less likely. Examples of the C-coordinated derivatives of oxazole (**170**) and isoxazole (**171**) are known [89JOM(372)287]. The complexes of composition  $CrL_2$  based on 3-methyl-5-phenyl- and 3,5-diphenylisoxazole were assigned a polymeric structure with the  $\eta^6$ -coordinated framework (78ZOB418). The other example is the interaction of the cyano complexes  $[M(CN)(cp)(dppe)]$  ( $M = Fe, Ru$ ) or  $[Fe(cp)(dppe)(CNH)]Br$  with *gem*-dicyanoepoxide to afford the oxazol-2-yl complexes with the C-coordination mode

[96JCS(D)3231]. 4-Methylthiazole (LH) reacts with  $[\text{Os}_3(\text{CO})_{10}(\text{MeCN})_2]$  to yield  $[\text{Os}_3(\mu\text{-H})(\text{CO})_{10}(\mu\text{-}2,3\text{-}\eta^2\text{-L})]$  in which thiazole is bridged to the cluster via the nitrogen and carbon atoms of the  $\text{N}=\text{C}$  bond [96JCS (D)1731]. Complex compounds of the Group VI elements (**172**) and (**173**)



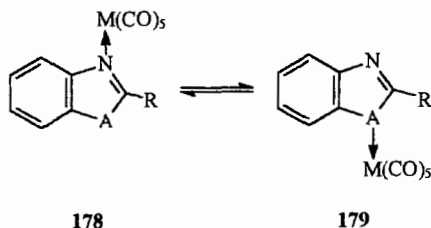
have predominantly  $\eta^1$  N-M bonds [82AG712; 83ZOB612; 84IZV1914; 88MI2; 89KK214; 90ICA(168)47; 91AJC1659, 91AX(C)2550, 91MI3; 94CB2381, 94IC490].

One of the frequently discussed problems is the coordination mode in complexes of benzo-2,1,3-thiadiazole (A = S) and its selenium analogue (A = Se), (**174**) or (**175**) (72ZOB592, 72ZOB2049). X-ray studies indicate that only the N-M coordination (**174**) is realized. The same mode is characteristic for the complexes of 1,2,3-thiadiazole and 1,2,3-selenadiazole (**176**). However, the X-ray analysis shows that the coordination via the A atom cannot be excluded, e.g., tellurium may serve as the donor site in the



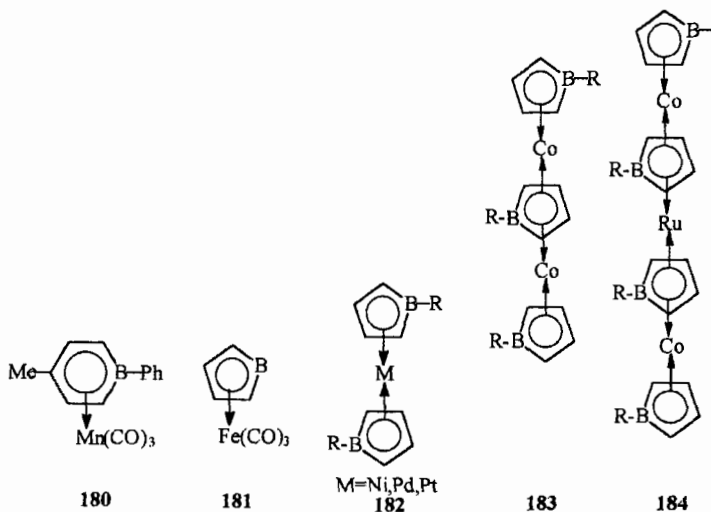
benzotellurazole ligand (**177**) (96KK376, 96KK512, 96MI6; 97MI3). Such a coordination mode may be related to a high donor activity of the tellurium atom (96MI24). It is important to obtain the X-ray data on the metal carbonyl complexes of benzothiazole and benzoselenazole, for which in solu-

tion the equilibrium of **178** and **179** is realized ( $M = \text{Cr, Mo, W}$ ). Reaction of 1,2,3-selenodiazoles with  $[\text{Co}(\text{C}_5\text{R}_5)(\text{CO})_2]$  ( $R = \text{H, Me}$ ) in toluene yields not the molecular complexes of type **174** but the diselenols with the general formula  $[\text{Co}(\text{C}_5\text{R}_5)(-\text{Se}-\text{C}(\text{R}')=\text{C}(\text{R}')-\text{Se}-)]$  where  $\text{R}' = \text{H, (CH}_2)_6, -\text{CH}=\text{CH}-(\text{CH}_2)_4, \text{H}_2\text{C}=\text{CH}-\text{CH}_2, \text{Ph}$  [93JCS(D)703].

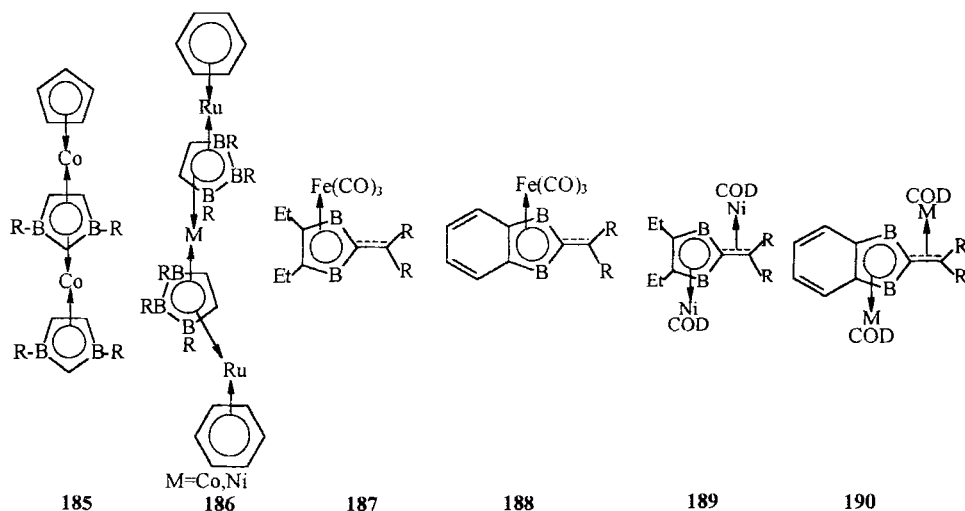


#### D. COMPLEXES OF FIVE- AND SIX-MEMBERED HETARENES CONTAINING ENDOCYCLIC ELEMENTS OF GROUPS III–IV

There are complexes of hetarene ligands with endocyclic boron atoms (96AOC209). Boroles are famous for their multidecker complexes. The triple-deckers are formed even for the complexes with organolithium compounds [95JOM(502)67]. Generally, boron analogies of pyrrole, pyridine, and azoles give rise to the following  $\pi$ -complex types: **180** (77CB1167), **181** [87JOM(319)311], **182**, **183** [87JOM(319)9], and **184**. The anionic sandwich of borabenzene is formed even in the reaction of the adduct of this hetero-



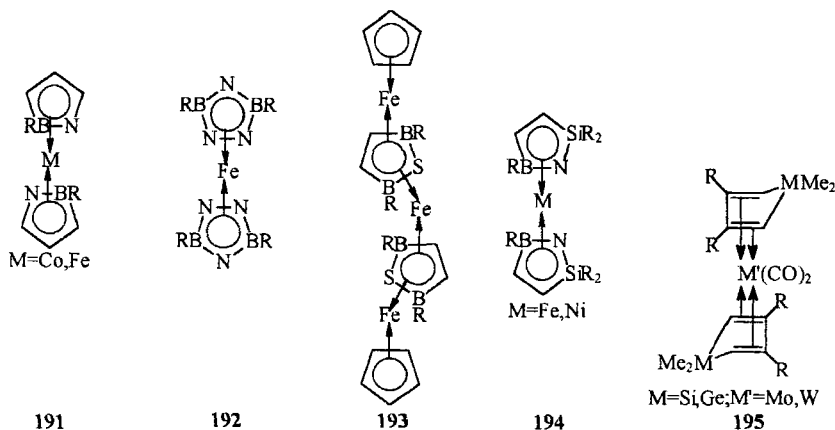
cycle with trimethylphosphine and  $\text{LiAlH}_4$  [96AG(E)292]. On the basis of  $\text{Cp}^*\text{Fe}(\text{C}_5\text{H}_5\text{BMe})$  by means of electrophilic stacking reactions with metal-containing species, a series of triple-deckers resulted, among them  $[(\mu\text{-C}_5\text{H}_5\text{BMe})(\text{FeCp}^*)_2]\text{PF}_6$ ,  $[(\mu\text{-C}_5\text{H}_5\text{BMe})(\text{FeCp}^*)(\text{RuCp}^*)]\text{CF}_3\text{SO}_3$  and  $[(\mu\text{-C}_5\text{H}_5\text{BMe})(\text{FeCp}^*)(\text{MCp}^*)](\text{CF}_3\text{SO}_3)_2$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) (96MI21, 96OM5236). 1,2,3,4-Tetramethyl-1,4-dibora-2,5-cyclohexadiene forms sandwiches as well as triple-deckers (96MI16). The five-membered hetarenes and diborafulvenes with several boron atoms may serve as  $\pi$ - ( $\eta^5$ -) ligands, e.g., **185** [85AG(E)943; 88PAC1345; 93MI3; 95JCS(D)1783, 95OM1911], **186**, and **187–190** (89CB633; 90CB2273; 94CB2393). The studies in this field have reached the stage of directed synthesis, e.g., the preparation of triple-deckers and sandwiches having planar  $\text{C}_2\text{B}_3$  units at one or both ends



(95JA12227), or synthesis of penta- and hexadeckers from the triple-decker building blocks (95JA12218). A similar coordination mode is typical for the boron-nitrogen ligands **191** (82CB732; 83CB951) and **192** (96MI23). The six-membered boron-nitrogen heterocycles form the widely represented complexes of borazines (77CCR185). The representatives of the  $\pi$ - ( $\eta^5$ -) complexes of the ligands containing boron and sulfur (silicon) ring atoms are **193** [80AG(E)746; 85JOM297] and **194** (82CB738).

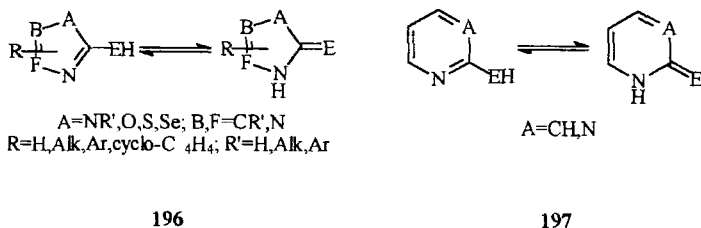
The silole and germole dianions possess delocalized  $\pi$ -systems. Monoanions of germole contain pyramidal germanium atoms and the delocalized diene portion of the ring [96AG(E)1002, 96JA10457]. Complexes in which the heteroatoms are the Group IV elements silicon or germanium are

mainly characterized by  $\pi$ - ( $\eta^4$ -) coordination (90CRV265) as a result of metal bonding to the two double bonds of the heteroring, e.g., **195**. For ger-mole the first  $\eta^5$ -complex has been prepared [93AG(E)1744].



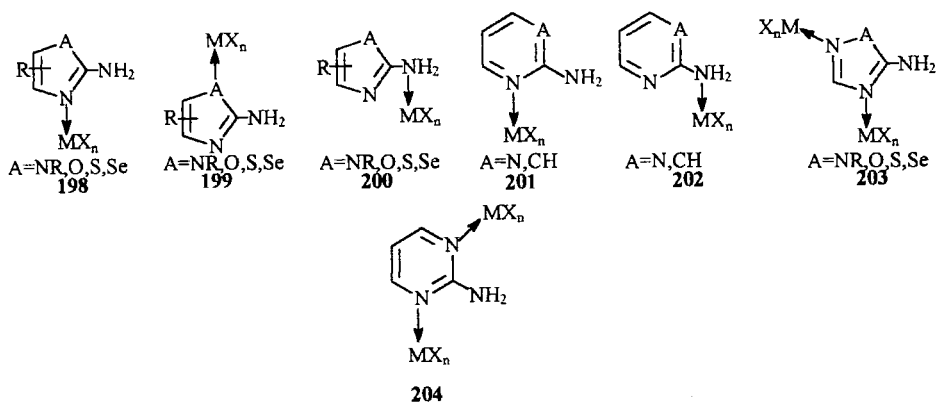
### E. COMPLEXES OF HETERENES CONTAINING EXOCYCLIC COORDINATION-ACTIVE SUBSTITUENTS

Coordination compounds of this type were prepared from amino-, hydroxy- and chalcogenohydrido- derivatives of azines and azoles (**12**, **196**, **197**) that show tautomerism (63AHC311; 72KGS1011, 72UK701; 76AHCS1, 76MI1; 84MI5; 96UK321), as well as the chelating ligands (**49** and **50**).



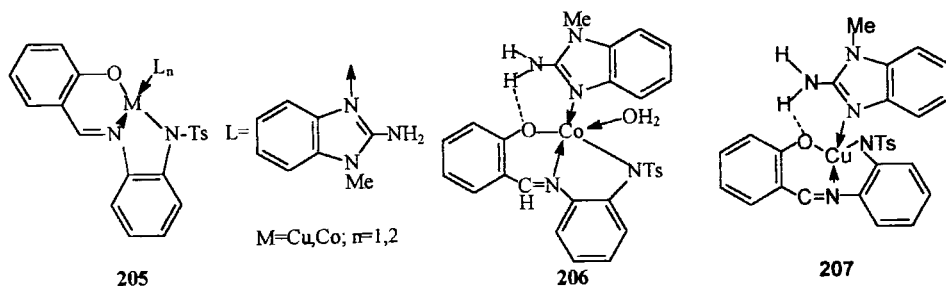
#### 1. Complexes of Amino Derivatives of Heterocycles

Amino heterocycles exist mainly as the amino tautomers (91H329). For the complexes of **196** and **197** structures **198–204** may be proposed. The common coordination mode is via the nitrogen atom of the pyridine type

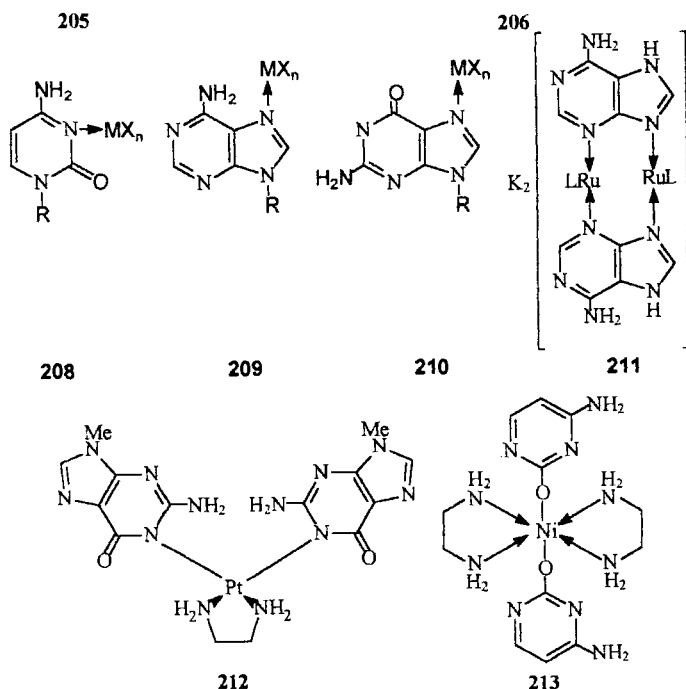


for the azole (**198**) and azine (**201**) heterocycles. According to X-ray data such coordination is observed in the complexes of 2-aminothiazole with cobalt (87ZK157) and zinc [93AX(C)592] chlorides, and with copper acetate (85TH1; 89ZSK155). The study of the complexes with copper acetate (**198**) by X-ray analysis and IR spectroscopy provided the reason for the decrease in the stretching vibrations of the  $NH_2$  group. The "test" for coordination via the amino group as indicated in **200** and **202** is the formation of  $N-H \cdots N$  intermolecular hydrogen bonds (87DOK1119; 89ICA177). This coordination mode stems from the quantum-chemical interpretation of the regioselective coordination in the metal complexes of 2-aminoazoles (95IZV2378, 95MI11; 96KK510). This is a continuation of the calculations on the free ligands (88KK299) that estimated the relative thermodynamic stability of linkage isomers **198–200**. The predominant coordination (**198**) of the proton and  $BH_3$  via the pyridine nitrogen atom follows from the results of these calculations (95KK684).

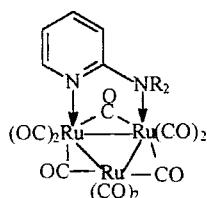
Localization of the coordination bond at the N atom (**198**) is characteristic of the adducts of 1-methyl-2-aminobenzimidazole with chelates of tridentate Schiff bases (**205**) in which the intramolecular hydrogen  $N-H \cdots O$



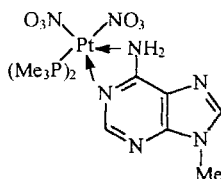
bond is formed (**206**, **207**). Structures **199** and **200** for the complexes of aminoisoxazoles were not confirmed by X-ray analysis. Complexes of aminoazoles with the bridging function (**203**) are described (91IC4858; 93ICA(205)53; 94ZSK164). Coordination via the endocyclic N atoms of the pyridine type is observed in complexes of 2-aminopyridines (**201**, A = CH) [93CSR55; 94IC728; 95JA3485; 96AX(C)1200], pyrimidines, (**202**, A = N) and (**204**, A = N) [90IC3027, 90TMC(L)23; 91POL873; 94IC3018; 95POL1553; 96AX(C)51], and the biological compounds, cytosine (**208**) [79MI1; 90AX(C)1645; 91IC884; 93JCS(D)669, 93JCS(D)1113; 94IC3169; 96POL63] and the purines, adenine (**209**) [92ICA(198)723; 93ICA(211)221] and guanine (**210**) [93ICA(210)167; 95AX(C)1769]. Purine (R = H) may form the dimeric ruthenium complex (**211**) [90ICA(176)241]. Bridging is followed by the deprotonation of the NH group of the imidazole ring and formation of the tetranuclear  $\eta^6$ -benzene-ruthenium(II) cluster [93ICA(206)15]. For guanine, coordination as in **211** is common, but other coordination modes are known (92IC2429). In the complex of 9-methylguanine with ethylenediamineplatinum(II), structure **212** is realized. The O coordination of cytosine in **213** is unexpected (90IC2568); the ligand here is in the enolate anion form.



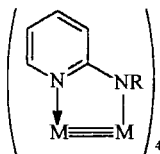
In the series of complexes of aminoazoles and -azines, evidence for coordination via the  $\text{NH}_2$  group (**200** or **202**) is practically absent, although such a coordination mode is not excluded. There are complexes of amino heterocycles in which a ligand is bonded to both donor sites, the nitrogen atom of the pyridine type and the unchanged or deprotonated amino group. In such complexes a multiple metal-metal bond (78IC3541; 93MI1) is often formed [90IC4033, 90IC5088, 90JCS(D)2201, 90JCS(D)3347; 91IC4611; 92POL13; 94OM4352, 94OM4360, 94POL2647, 94POL2933; 95ICA(237) 103; 96JCS(D)299]. Species with  $\eta^2:\mu$  coordination and simultaneous bonding of the endocyclic and amino nitrogen atoms are observed in the ruthenium cluster **214**, in the trinuclear adduct  $\{[\text{Ru}(\text{III})\text{Ru}(\text{III})\text{Ru}(\text{II})\text{OAc}_6\text{L}_3]\text{L}_3'\}$ , where  $\text{L} = 2\text{-aminopiperazine}$  and  $\text{L}' = \text{EDTA}$ , and in the platinum(II) complex of 9-methyladenine with trimethylphosphine (**215**). The metal clusters (**216**) contain the deprotonated amino group. Among the



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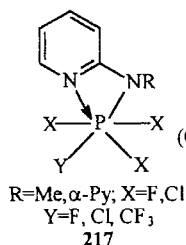


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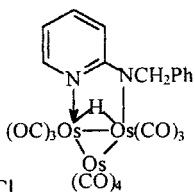


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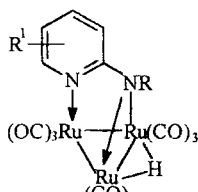
complexes with such an N-H group are both mono- and polynuclear complexes. The mononuclear species are exemplified by the complexes of 2-methylamino- and 2-(2'-pyridyl)aminopyridines with halides and  $\text{CF}_3$ -substituted derivatives of the pentavalent phosphorus (**217**). In clusters **218**, the NR nitrogen atom may be bonded simultaneously to two metal atoms, forming the trinuclear clusters **219**. Compounds in which the  $\text{NH}_2$  hydrogen atoms are replaced by a metal are known for some other heterocycles, for instance cytosine and 3-aminopyridine (90JA1590). The ruthe-



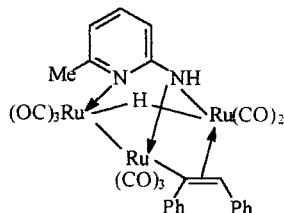
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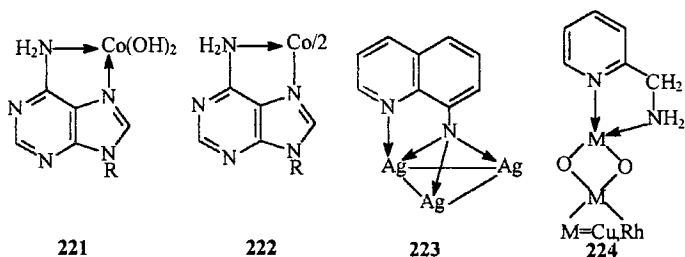


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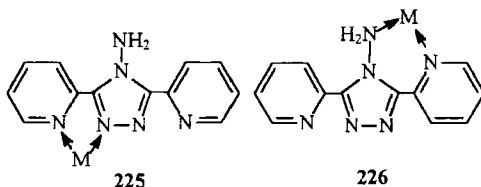


nium cluster of the same pattern (**220**) is known, and its reaction ability has been studied in detail [96JOM(511)103].

Involvement of two nucleophilic nitrogen atoms is thus typical for the amino heterocycles. The mutual disposition of the pyridine and amine nitrogen atoms allows the formation of chelate structures for the cobalt complexes of purine, **221** and **222**. Structures with the *N, N'*-five-membered metal cycles were proven for the tri- and tetranuclear complexes of silver(1) with 8-aminoquinoline (**223**) (92IC4370), and polymeric copper- and rhodium-acetate clusters (**224**). Another coordination mode can be found in the complexes of 4-amino-3,5-bis(pyridin-2-yl)-1,2,4-triazole, (**225** or



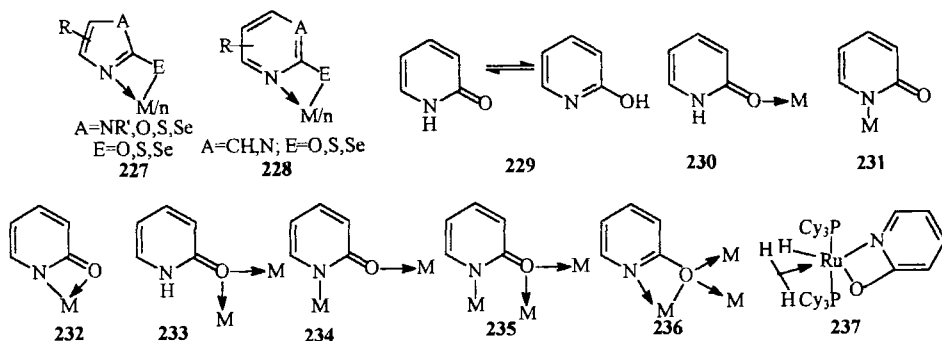
**226**) [92IC198; 93ICA(214)41]. In the complexes of bis[4-amino-3,5-bis(pyridin-2-yl)-1,2,4-triazole]bis(7,7',8,8'-tetracyanoquinodimethanido) copper(II), structure **225** is present, whereas in the complexes of the same ligand with ruthenium dichloro dicarbonyl,  $\text{Ru}(\text{CO})_2\text{Cl}_2$ , both isomers co-exist. Isomer **225** is the product of interaction of the ligand and  $\text{Ru}(\text{CO})_2\text{Cl}_2$  in methanol, and **226** is obtained when LiBr is added to the reaction mixture.



## 2. Complexes of Hydroxyhetarenes

A variety of the structures is observed for the complex compounds prepared from ligands **196** and **197** containing the O (OH) exocyclic framework. Compared to the amino heterocycles, they are characterized predominantly by the chelate structures **227** and **228**. The coordination

chemistry of the oxygen-containing ligands presented by the complexes of **229** is described in reviews and will not be considered. This ligand is capable of forming mono- (**230–232**), di- (**233, 234**) and tri- (**235, 236**) nuclear complexes. A bridging function is fulfilled by **229** in complexes with

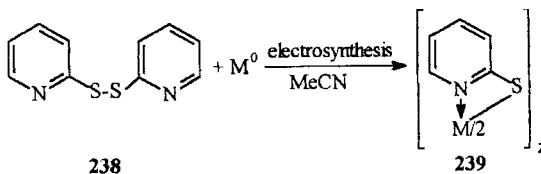


metal–metal multiple bonds. Recent examples are complexes **237** (96OM3471) and NBu<sub>4</sub>[Pt(C<sub>6</sub>F<sub>5</sub>)<sub>2</sub>(8-hydroxyquinaldine)] (96IC6009). Among the chelates with hetarene fragments, the complexes prepared from 2-*O*-hydroxy(*N*-tosylamino)azoles are important [76ZOB670, 76ZOB2706; 98ZOB496].

### 3. Complexes of Mercaptohetarenes and Their Analogs

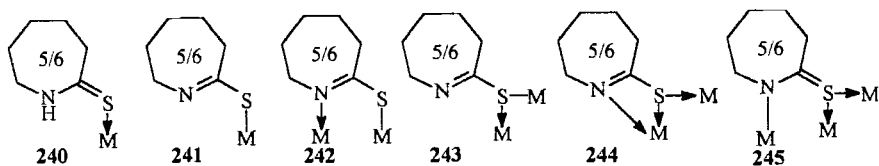
These are reviewed in Raper [96CCR(153)199]. The chelate structures **227** and **228** represent complexes of 2-mercapto (2-thione) derivatives of the aromatic nitrogen heterocycles. These compounds can be prepared both by interacting 2-mercaptoazoles (2-thiones) (azines) with metal salts [91ICA(188)7; 92ICA(196)81; 93JCS(D)430, 93KK131; 94AOC397, 94AX(C)1196, 94TMC(L)385; 95IC60] and by electrosynthesis from the zero-valent metals [90ZN(B)1632; 93POL2241; 94JCS(D)1115; 95POL17, 95POL2841]. 2-Mercaptopyridine reacts with *fac*-IrH<sub>3</sub>(PPh<sub>3</sub>)<sub>3</sub> to yield Ir(H)<sub>2</sub>(η<sup>2</sup>-SPy)(PPh<sub>3</sub>)<sub>2</sub> (96IC3001). Further reaction of 2-mercaptopyridine and HBF<sub>4</sub> with the product affords [IrH(η<sup>1</sup>-SC<sub>5</sub>H<sub>4</sub>NH)(η<sup>2</sup>-SC<sub>5</sub>H<sub>4</sub>N)(PPh<sub>3</sub>)<sub>2</sub>]BF<sub>4</sub>. Adducts **54** are formed in the presence of bases (pyridine, bipyridine, *o*-phenanthroline, and diphenylphosphinomethane). The transformation of **238** to **239** may be achieved by electrosynthesis and similarly for the zero-valent lanthanides (samarium, yttrium) in THF by the chemical means [95JOM(501)263].

Pyridine-2-thione (LH) reacts with [Mo(CO)<sub>3</sub>(MeCN)<sub>3</sub>] to yield binu-

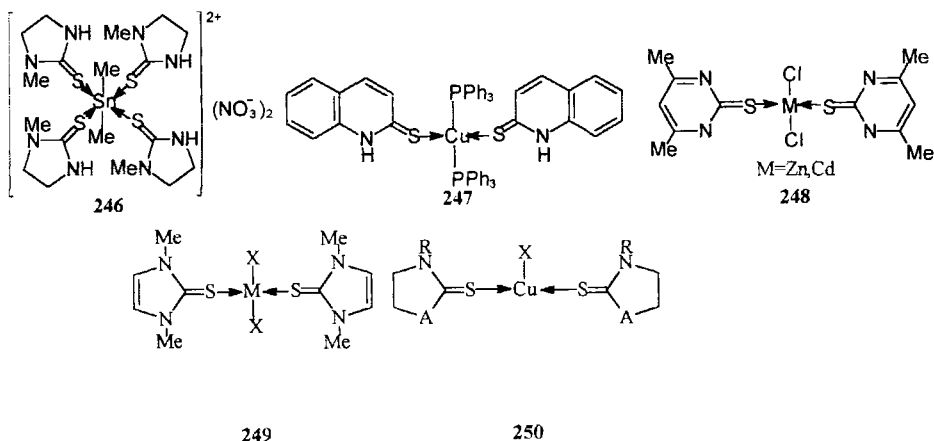


clear  $[\text{Mo}(\mu\text{-L})_2(\text{CO})_4(\text{PPh}_3)_2]$ ,  $[\text{Mo}_2(\mu\text{-L})_2(\text{CO})_5(\text{PPh}_3)]$ , and  $\text{Mo}_3(\mu\text{-L})(\mu_3\text{-L})_2(\text{CO})_6$  [96JOM(514)183]. 4,6-Dimethyl-2-mercaptopyrimidine reacts with  $\text{Cp}_2\text{ZrMe}_2$  to yield the thiolate alkylzirconocene complex with a four-membered chelate ring (96OM4725). The species  $\text{MH}(\text{CO})$  (quinoline-8-thiolate) ( $\text{M} = \text{Ru}, \text{Os}$ ) has been studied (96OM4423). Reaction of the dilithium salt of 2,6-pyridine-2-thiolate with  $[\text{M}(\mu\text{-Cl})(\text{diolefin})_2]$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) gives the tetranuclear  $[\text{M}_4\mu_4\text{-PyS}_2](\text{diolefin})_4$ . This complex contains two *S,N,S*-tridentate 2,6-dimercaptopyridine ligands bridging all four metal centers. One of the sulfur atoms is bonded to one metal atom; the other is attached to two different metal centers (96IC1782).

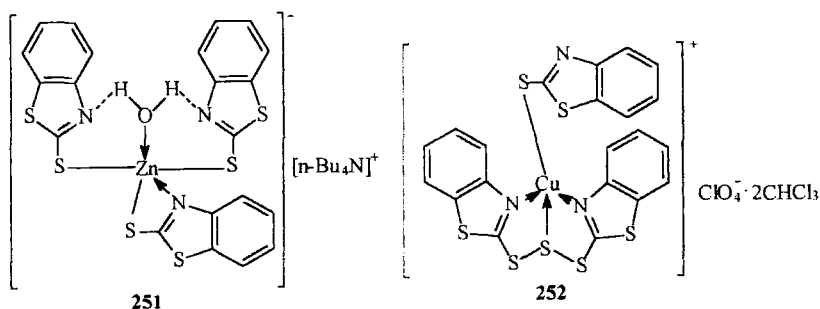
The presence of N- and E-donor sites and prototropic tautomerism led to different structures of the complexes of mercaptoazoles and mercaptoazines (240–245). In 240 the ligand is monodentate; it occurs in complexes



of composition  $(\text{LH}_m)\text{MX}_n$  [86JOMC25; 90IC4005; 91ICA(184)43; 92ICA(191)75; 93JCOC111; 94AX(C)54, 94POL273; 96ICA(345)119]. Complexes prepared from 1-methyl-2(3*H*)-imidazoline thione (246), quinoline-2-thione (247) and 4,6-dimethylpyrimidine-2-thione (248) are known. Examples of  $=\text{S} \rightarrow \text{M}$  coordination are observed in complexes with a fixed thione group as in 1,3-dimethyl-2(3*H*)-imidazole thione (249) [92ICA(192)51], *N*-alkyl-imidazolidine-2-thione (250,  $\text{A} = \text{NR}$ ) and thiazolidine-2-thione (250,  $\text{A} = \text{S}$ ) [95JCS(D)115]. Benzimidazole-2-thiol ( $\text{H}_2\text{L}$ ) reacts with  $[\text{M}(\mu\text{-Cl})_2(\text{cod})_2]$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) to give  $[\text{MCl}(\text{H}_2\text{L})(\text{cod})]$  where the ligand is S coordinated. Reaction of the same ligand with  $[\text{M}(\text{acac})(\text{cod})]$  gives  $[\text{M}_2(\mu\text{-HL})_2(\text{cod})_2]$  ( $\text{M} = \text{Rh}, \text{Ir}$ ), in which two metals are bridged in a  $\mu_2\text{-N,S}$  fashion. Further reaction of these bridged complexes with  $[\text{M}(\text{cod})(\text{Me}_2\text{CO})_2]^+$  gives the trinuclear  $[\text{M}_3(\mu\text{-HL})(\text{cod})_3]$ , whereas their reaction with  $[\text{M}'_2(\mu\text{-OMe})_2(\text{cod})_2]$  yields  $[\text{MM}'(\mu\text{-$

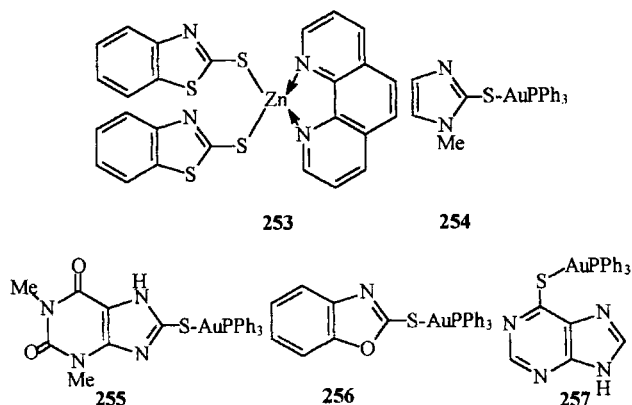


$L(\text{cod})_2]_2$  ( $M, M' = \text{Rh}, \text{Ir}; M = \text{Ir}, M' = \text{Rh}$ ) (96IC4360). The number of complexes having structure **241** is much less. The thiol form of the ligand does not lead to chelate structures. Such a monodentate S coordination is observed in the complex anion of  $\{[n\text{-Bu}_4\text{N}]^+[\text{ZnL}_3]^- \text{H}_2\text{O}\}$  (**251**) and the cationic complex of the trisulfide derivative of benzothiazole (**252**).

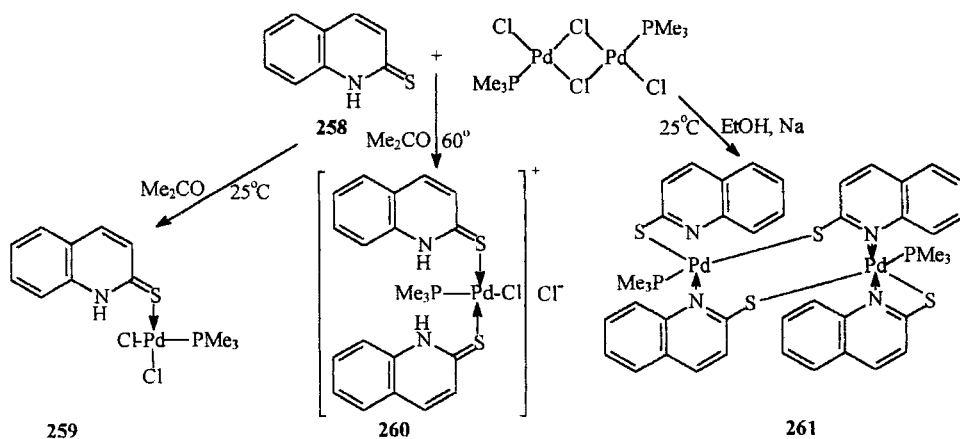


Mononuclear complex formation was confirmed for the adduct of zinc(II) salt with 2-mercaptobenzothiazole and *o*-phenanthroline (**253**). The  $\eta^1\text{-S}$  coordination is observed in the complexes of triphenylphosphine gold with 2-mercapto-1-methylimidazole (**254**) (88JOM119), 8-mercaptotheophylline (**255**) (91IC3743), 2-mercaptobenzoxazole (**256**) [94AX(C)1420], and purine-6-thiol (**257**) (94AJC577).

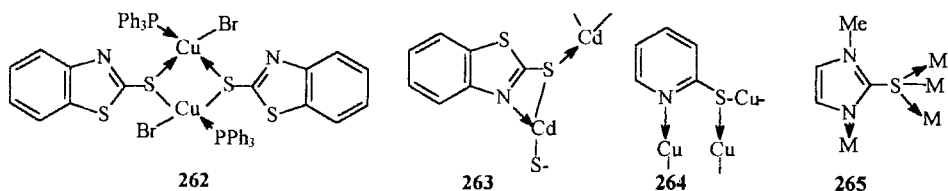
Structures **242** with bridging N,S coordination are common for binuclear complexes [90ICA(174)209; 91ICA(183)179, 91MI4; 92IC4823; 94CB2355; 95IC988, 95ICA(237)143; 96JCS(D)2047]. Depending on the nature of the



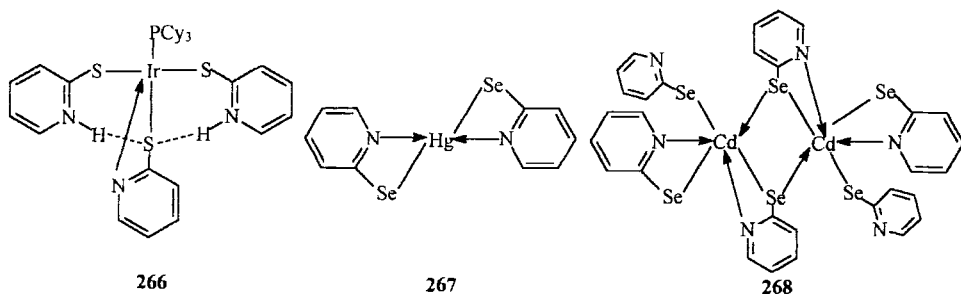
solvent, temperature, and pH, the same ligand **258** may form the mono-S-coordinated adducts **259** and **260** with the thione tautomeric form, as well as binuclear complex **261**, in which the thiol and bridging N,S-bonding modes operate simultaneously. S,S coordination (**243**) [85ICA(98)L21, 85JCS(D)2101; 88POL1401; 92AG(E)1253; 96POL2127] may be exemplified by the copper benzothiazole dimer (**262**). Complex compounds of 2-mercaptohetarenes coordinated in the  $\eta^2(\text{N},\text{S}) : \eta^1(\text{S})$  fashion (**244**) [90POL541; 94AX(C)1195] may be illustrated by the framework **263** of the polymeric cadmium complex of 2-mercaptobenzothiazole. Trinuclear complexes **245** are scarce [88JCS(D)235, 88JCS(D)2193; 90JCS(D)1493, 90JCS(D)2165; 92JCS(D)2559; 94POL2085]. The fragment **264** occurs in the hexanuclear complex of copper(I) with 4,6-dimethyl-2-mercaptopyrimidine. In the 12-nuclear cluster  $[\text{Cu}_{10}^{\text{I}}\text{Cu}_2^{\text{II}}(\text{C}_4\text{H}_5\text{N}_2\text{S})_{12}(\text{MeCN})_4]$ , where



$C_4H_5N_2S$  is the anion of 1-methyl-2-mercaptoimidazole, the thiol sulfur may participate in coordination with three copper atoms (**265**) [80JCS(CC)867]. In the iridium complex cation **266** with 2-mercaptoypyri-

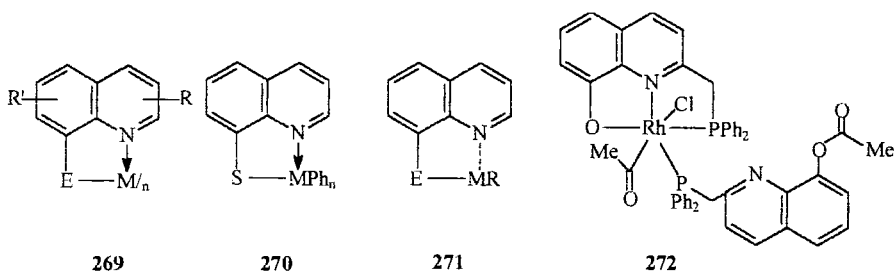


dine, three ligands are bound to the metal differently: two by the  $\eta^2$ -S-monodentate and one by the  $\eta^2$ -N,S-chelate modes [94JCS(CC)2021]. The pyridinic nitrogen is protonated and participates in intermolecular hydrogen bonding. Complexes of the selenium-containing ligands **227** and **228** are scarce. Mercury complex of 2-pyrineselenol has a chelate structure (**267**) (94IC3711), whereas in the cadmium dimer, chelate (**228**) and bridging (**243**) coordination modes coexist (**268**).



Complexes of 8-hydroxy- and 8-mercapto-quinolines (**269**, E = O, S) (92MI5; 93MI8; 94MI3–94MI5; 95MI10; 96IC5249, 96MI17, 96MI18) are exemplified by three-ring chelates (E = O,  $n = 3$ ) of indium(III), gallium(III), thallium(III), and cobalt(III) as well as of osmium(III), ruthenium(III), and rhodium(III). All the complexes are octahedral. Divalent nickel, cobalt, copper, zinc, and cadmium form the bis-thioxinates. The mixed-valent complexes of vanadyl with 8-mercaptoquinoline are known (92AG1380). In one of them,  $(VL_3)^-(PPh_4)^+$ , vanadium has the oxidation number of two, whereas in the neutral species  $VL_3$ , the oxidation number of vanadium is three. The organometallic derivatives of oxine (78AJC537; 80ZSK87; 83ZSK130; 88MI1; 89MI1) and thioxine [86AX(C)1138; 90MI3; 92MI6, 92MI9] are of interest. In the complexes **270** the chelate structure is com-

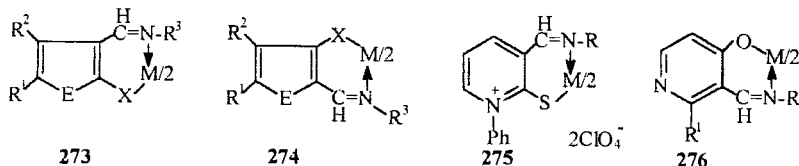
mon. Chelates of titanium, zirconium and hafnium,  $M(\eta^5-C_5H_5R)ClL_2$  ( $R = H, Me, SiMe_3$ ,  $L = 8\text{-hydroxyquinolinato- or } 5\text{-chloro-8-hydroxyquinolinato}$ ) (95ZAAC1761) are characterized by a coordination number of eight and geometry close to dodecahedral. However, for complexes with phenylmercury- and triphenylphosphine gold frameworks (**271**), the less common mode is postulated: only one covalent  $M-E$  bond and a secondary  $M\cdots N$  bond. The structures of the complexes of 8-hydroxyselenoquinoline are uncertain, although the chelates (**269**,  $E = Se$ ) have been known for a long time [89KK715]. Complexes of the tellurium-containing ligands **227** and **228** are apparently not described [92JCOC237; 93AHC(58)47; 95JCOC207]. The ligand 2-[(diphenylphosphino)methyl]quinolin-8-ol acetate reacts with  $[(cod)_2Rh(\mu-Cl)]_2$  to yield a remarkable product with a mixed coordination mode (**272**) (95OM5171).

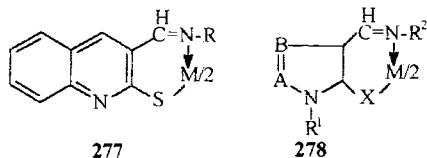


#### 4. Complexes of Chelating Heterene Ligands

Data have accumulated on the influence of heteroannulation and introduction of the heteroaromatic substituents to the chelating ligands on the structure of the complex compounds.

a. *Heteroannulation.* The most widespread complexes are azomethine chelates containing five-membered heterocycles (**273**) (72UK679; 76KK115; 81KGS1484) and (**274**) (76KK1514; 77ZSK1049; 78KK1499; 79KK1088; 87ZOB2342; 91KK192; 93MI4), azines (**275**) [86ICA121; 89JCS(D)1979], (**276**) (83ICA135; 86CPB3553), and (**277**) (91MC78), and azoles (**278**) [70ZOB2338; 72ZOB926; 75ZOB202; 79ZOB417; 89

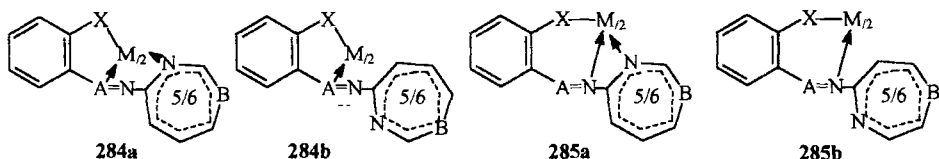
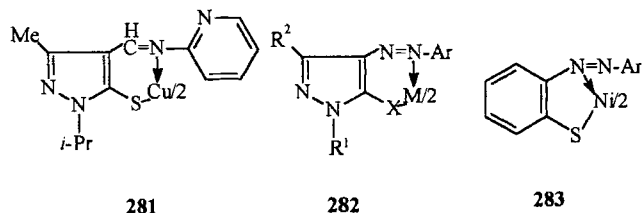
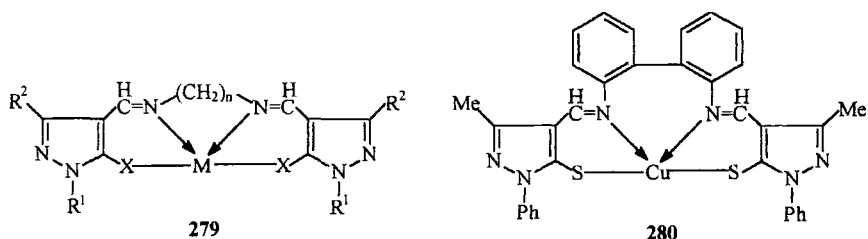




JOM(368)303; 95IC4467, 95JCS(D)362, 95MI4; 96JCS(D)1215, 96MI5, 96MI7; 97DOK(355)777, 97DOK(356)212] annulated to the coordination unit. Annulation of the heterocycles leads to chelates **273** and **274**. Their structures depend on the nature of E, X, and  $R^{1-3}$ , as well as the mutual disposition of the X and C=N. Thus, the azomethine complexes of thiophene (**273**; E = X = S;  $R^3$  = cyclo- $C_6H_{11}$ ;  $R^1$  = Et; M =  $Co^{II}$ ,  $Ni^{II}$ ) are tetrahedral. However, the nickel complex (**274**; E = X = S;  $R^1$ ,  $R^2$  = cyclo- $C_4H_4$ ;  $R^3$  =  $C_4H_9$ ; M = Ni) is *trans*-planar. Nickel complexes (**274**; E = O; X = S;  $R^3$  = Ph;  $CH_2Ph$ ;  $R^1$ ,  $R^2$  = cyclo- $C_4H_4$ ) are tetrahedral. Complex **275** has a pyramidal structure, whereas copper chelates **276** have a distorted tetrahedral structure. Zinc complex **277** is tetrahedral. Annulation of the pyrazole ring (**278**; A = N; B =  $CR^2$ ) leads predominantly to tetrahedral chelates irrespective of the nature of X,  $R^{1,2}$ , and M [91POL180; 95ICA(228)237], and to the chelates of zinc, cadmium, and mercury when the formation of tetrahedral structures is intrinsic (88KK237; 89POL569; 94RCR289). Complexes **279** are tetrahedral, although generally *cis*-planar structures are expected. For the planar nickel complexes with the coordination units  $MN_4$  (X = NH) and  $MN_2S_2$  (90IZV327), there are distinct tetrahedral distortions. These are characteristic for the copper complexes **279** (X = NH; M = Cu;  $n$  = 2–5;  $R^1$  = Me;  $R^2$  = Ph), 280 [86JCS(CC)699], and 281 (92MC30). The palladium complexes of the pyrazole azomethines (**278**; A = N; B = CMe; X = S; M = Pd) have the *cis*-(R =  $\alpha$ -py) (93DOK54) or *trans*-(R = cyclo- $C_6H_{11}$ ) [91ICA(180)L51, 91MI1] planar configurations. Complexes of 4-azo-5-amino-(hydroxy-, mercapto-) pyrazolones (**282**) belong to the heteroannulated chelates [72MI1; 88ZOB1440; 94TMC(L)319]. The nickel complexes of amino- (**282**; M = Ni; X = NH) and oxy- (**282**; M = Ni; X = O) azopyrazolones are tetrahedral in the crystalline state, but similar mercapto derivatives (**282**; M = Ni; X = S) are polymeric and octahedral in the solid state but planar in solution. The flattening may be related not only to the nature of X but the change of the number of edges of the ring [75JCS(CC)105; 80KK954]. Thus, in aromatic complexes (**283**) the five- but not the six-membered metal rings are formed.

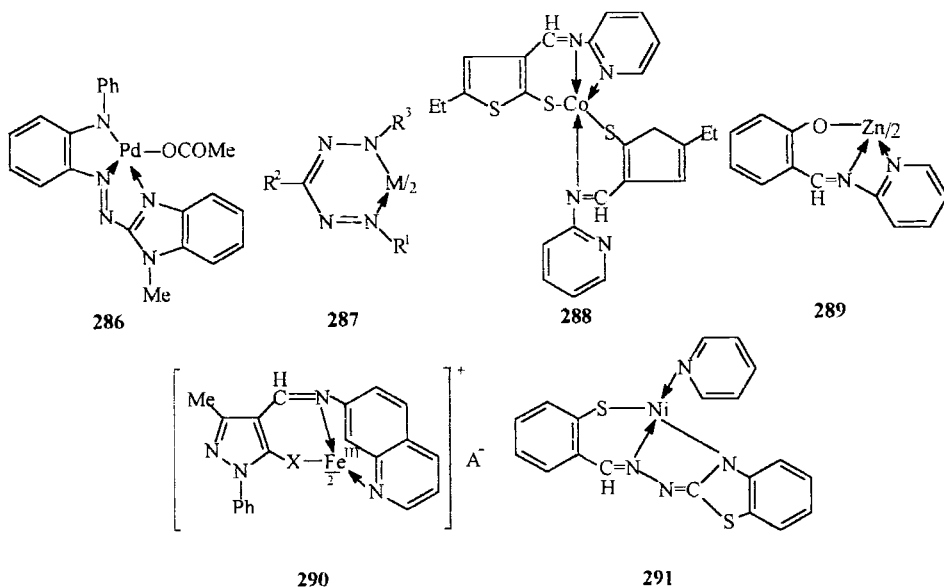
**4.2. Heterosubstitution.** Application of nitrogen-containing heteroaromatic rings as substituents in the chelating ligands leads to the structural changes. This is characteristic for the complexes of hetarylamino (oxy) azo



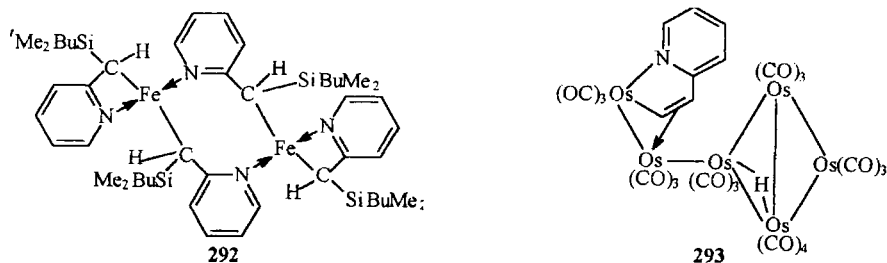


ligands (**284** and **285**) [67JCS(A)278; 70DOK614; 71DOK341; 80IC2052; 85MI2; 88KK94, 88KK259; 89KK1027; 91KK886; 96MI10] and hetarylformazanes (**53**). For the hetaryl amino azo compounds (**284**), the structure with two five-membered metal rings (**286**) is known; the pyridinic N atom participates in coordination. The same coordination mode is observed in the chelates of hetarylformazanes. In contrast to the planar aromatic analogs with a six-membered metal ring **287**, octahedral polyhedra with two five-membered coordination units are formed (**53**) (89ZOB2362; 92KK312). The problem of coordination via the nitrogen-containing hetaryl substituents in the azomethine complexes (**278**,  $R^2 = \text{Het}$ ; **281**; **284**,  $A = \text{CH}$ ) has been discussed. It appeared that the hetarene substituent often does not take part in coordination, and depending on the nature of the metal, planar or tetrahedral polyhedra are formed [88ICA201, 88JCS(D)1059; 89POL2543; 93ZOB1144]. However, structures **288** and **289**, in which the heterocyclic nitrogen atom is bound to the metal as in **285a** ( $A = \text{CH}$ ;  $X = \text{O}, \text{S}$ ) are possible (94KK824). In both structures the distances  $M-N_{\text{py}}$  are enhanced compared to the normal values and unusual polyhedra are formed, such as one- (**288**) or double-capped (**289**) tetrahedra. Such bonding is known for the quinolylazomethine complex **290** ( $A =$

$\text{FeCl}_4^-$ ;  $\text{X} = \text{S}$ ) used to model the active sites of the nonporphyrine iron proteins with the N,S-ligand environment [96MI8; 97JCS(CC)1711]. Additional metal cyclic structures are formed upon introduction of an azole framework to the hydrazone systems (**291**) (92MI8), in which the imino tautomer of the benzothiazole is fixed.



**4.3. Other Chelating Heteroarene Ligand Systems.** Here only some recent examples and trends to study the reaction ability of metal chelates leading to new products and important materials are presented. An exotic chelate (**292**) was prepared by the reaction of an N-functionalized lithium agent with  $\text{FeCl}_2$  [96OM1785]. Cluster **293** [96JOM(513)27] is of interest. Pyridine-2-carboxylic acid (HL) on reaction with  $[\text{RhCpCl}_2]_2$  and MeONa gives  $[\text{RhCpCl}]$  [95JCS(D)3709]. The chelates of 5-phenyl-3-isoxazolecarboxylate with  $\text{Co(II)}$ ,  $\text{Ir(III)}$ ,  $\text{Ru(II)}$ , and  $\text{Pd(II)}$  are known [96ZN(B)581].



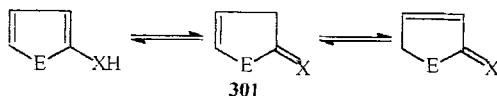


donor. The N-donor function is realized as a result of interaction with  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  (96OM3170). 2-(Diphenylphosphino)pyridine may be a part of the ligand *trans*- $\text{Fe}(\text{CO})_3(\text{Ph}_2\text{Py})_2$  that affords a series of the binuclear complexes  $(\text{OC})_3\text{Fe}(\mu\text{-Ph}_2\text{Ppy})_2\text{MX}_n$  ( $\text{MX}_n = \text{Mn}(\text{SCN})_2, \text{Co}(\text{SCN})_2, \text{CoCl}_2, \text{NiCl}_2, \text{Mo}(\text{CO})_3, \text{Zn}(\text{SCN})_2, \text{ZnCl}_2, \text{Cd}(\text{SCN})_2, \text{CdCl}_2, \text{HgCl}_2, \text{HgI}_2, \text{AgClO}_4, \text{SnCl}_2$ ) [96JOM(516)1]. Often both functions are simultaneous. 3,5-Bis(diphenylphosphino)methylpyridine reacts with  $\text{HRh}(\text{PPh}_3)_4$  to form  $\text{Ph}_3\text{PRhL}$  and with  $(\text{PhCN})_2\text{PdCl}_2$  to form  $\text{LPdCl}$ . The coordination is of the P,P,C type with the pyridine N atom intact (96IC1792).

The pyrrole ring participates in the formation of hetaryl chelates as a part of porphyrines, phthalocyanines (93MI2), corroles, corrines, and other macrocyclic ligands [87MI5; 96AX(C)876]. The latter may include furan and other heterocycles [87MI6; 90MI2; 95CRV273, 95CRV2529, 95CRV2725, 95JCS(P2)85; 96AG1314, 96AG1677]. However, their detailed consideration is beyond the limits of this publication. The bulk of information on the coordination compounds of pyrazolylborates was recently reviewed in Kitajima and Tolman (95PIC419).

## V. Conclusion

We have attempted to cover the problems of the chemistry of  $\sigma$ - and  $\pi$ -coordinated five- and six-membered heteroaromatic compounds. Omitted are the nitrogen-, phosphorus- (78S57; 79DOK1130; 84MI10), nitrogen-, selenium- (84MI7, 84MI8), and nitrogen-, tellurium- (84MI9; 86MI5; 96IC9) ligands. The problem of competitive coordination for such  $\sigma, \pi$ -ligands is not well studied. The possibility of application of the five- and six-membered metal-containing ligands is of interest (84MI1, 84MI2). The problem of the interaction of amino- (oxy-, mercapto-) derivatives of the five-membered heterocycles subject to tautomerism (**301**) (84MI3, 84MI4) with metal salts has not been studied extensively.



Saturated heterocycles are important ligands. They are flexible models for the problem of competitive coordination of the hard and soft acids with the nonconjugated donor sites. Analysis of these problems is of interest for the chemistry of complex and heteroaromatic compounds. The number of publications in the 1990's shows that the interest to the problems analyzed in the present review is still enormous.

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68JOM359  
68MI1  
69AX(B)842  
69CCR463  
69RTC1451  
70AX(B)521  
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70JCS(A)2558  
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# Synthesis of Amino Derivatives of Five-Membered Heterocycles by Thorpe–Ziegler Cyclization

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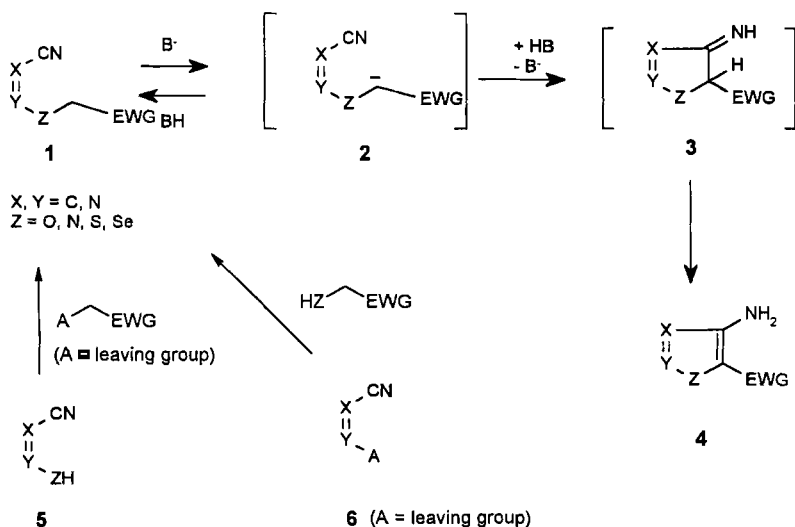
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I. Introduction .....	79
II. Synthesis of 3-Aminofurans .....	80
A. Synthesis of Monocyclic 3-Aminofurans .....	80
B. Synthesis of Annulated 3-Aminofurans .....	82
III. Synthesis of 3-Aminopyrroles .....	85
A. Synthesis of Monocyclic 3-Aminopyrroles .....	85
B. Synthesis of Annulated 3-Aminopyrroles .....	89
IV. Synthesis of 3-Aminothiophenes .....	96
A. Synthesis of Monocyclic 3-Aminothiophenes .....	96
B. Synthesis of Annulated 3-Aminothiophenes .....	100
V. Synthesis of 3-Aminoselenophenes .....	111
VI. Synthesis of Aminoazoles .....	113
References .....	116

## I. Introduction

One of the most convenient methods for the synthesis of functionalized amino heterocycles especially five-membered heteroaromatics (**4**), is the Thorpe–Ziegler cyclization (Scheme 1). A nitrile (**1**) undergoes ring closure by intramolecular addition of a deprotonated methylene group (EWG represents an electron-withdrawing group such as CN, COR', COOR', CONR'R'', NO<sub>2</sub>, electron-deficient aryl, or heteroaryl) onto the cyano group followed by a 1,3-H shift in the intermediate **3**. There are two principal routes to precursors **1**: the introduction of a CH<sub>2</sub>–EWG moiety by alkylation of compounds **5** and the substitution of a leaving group A in compounds **6** by HZCH<sub>2</sub>EWG. Thorpe–Ziegler cyclizations are mostly catalyzed by bases, although acid catalysis (e.g., Vilsmeier conditions) have also been used. A num-



SCHEME 1

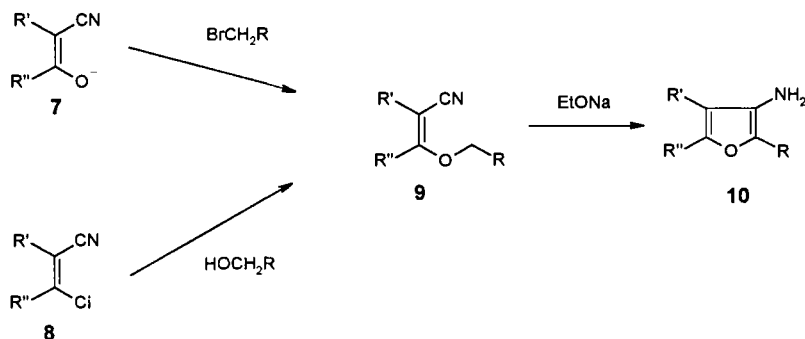
ber of reviews on Thorpe-Ziegler reactions have been published (67OR1; 70MI1; 80C101; 82MI1; 85MI1; 87MI1; 92MI1). Some are devoted to applications of the Thorpe-Ziegler reaction for synthesizing five-membered heterocycles (80C101; 85MI1). A recent review on 3-cyanopyridine-2(1*H*)-ones, -thiones and -selenones (92MI1) contains numerous examples of Thorpe-Ziegler syntheses of furo-, thieno-, and selenophenopyridines.

The present review covers the Thorpe-Ziegler syntheses of 3-aminofurans, 3-aminopyrroles, 3-aminothiophenes, 3-aminoselenophenes, and diverse aminoazoles as well as the corresponding annulated systems that appeared from 1983 to 1996 but excludes examples considered in the 3-cyanopyridine review (92MI1). Moreover, examples are included that do not report a separate Thorpe-Ziegler cyclization but are likely to involve this type of reaction (e.g., cases in which precursors **1** were not isolated and identified but directly formed in the reaction mixture). Special attention is paid to synthetic aspects, although some reaction mechanisms are discussed too.

## II. Synthesis of 3-Aminofurans

### A. SYNTHESIS OF MONOCYCLIC 3-AMINOFURANS

Investigation of the cyclization of *O*-alkylated cyanoenols (**9**) [ $R' = \text{Ar}$ , CN,  $R'' = \text{Ar}$ , H or  $R'R'' = (\text{CH}_2)_4$ ] in the presence of sodium ethylate revealed (84LA1702) that acylmethyl substituents ( $R = \text{Ar}'\text{CO}$  or  $\text{COMe}$ )

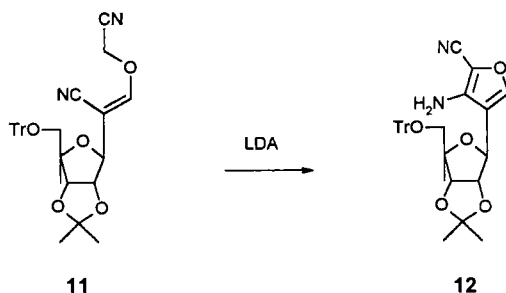


SCHEME 2

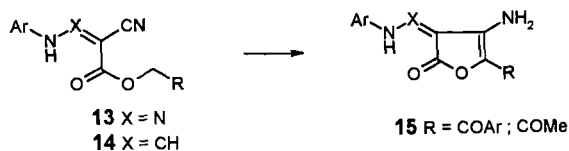
allowed a smooth Thorpe-Ziegler cyclization to 3-aminofurans (**10**), whereas less CH-acidic esters (**9**;  $\text{R} = \text{COOEt}$ ,  $\text{R}' = \text{Ar}$ ) gave very poor yields and 4-nitrobenzylethers (**9**;  $\text{R} = 4\text{-nitrophenyl}$ ,  $\text{R}' = \text{CN}$ ) resisted ring closure altogether. The starting materials (**9**) were accessible either from 3-hydroxyacrylonitriles (**7**) or from 3-chloroacrylonitriles (**8**) (Scheme 2).

Lithium diisopropyl amide (LDA) assisted Thorpe-Ziegler cyclization of cyanoenolethers (**11**) was used to synthesize the ribose-C-glycoside **12**, which was further transformed into a furo[3,2-*d*] pyrimidine (86TL815; 90MI1). Other bases such as  $\text{NaOEt}$ , 1,5-diazabicyclo[4,3,0] non-5-ene (DBN), *t*-BuOK or *n*-BuLi that were successfully used in pyrrole syntheses (see Section III.A) were not suitable for this furan formation (Scheme 3).

4-Aminofuran-2-ones (**15**) ( $\text{R} = \text{COAr}$ ,  $\text{COMe}$ ) could be synthesized by Thorpe-Ziegler cyclization of acylmethyl esters **13** and **14** in the presence of  $\text{NEt}_3$  and  $\text{NaOEt}$ , respectively. However, the less acidic ethoxycarbonylmethyl compounds **13** and **14** ( $\text{R} = \text{COOEt}$ ) or cyanomethyl esters ( $\text{R} = \text{CN}$ ) failed to ring close (84LA1702) (Scheme 4). The starting esters could



SCHEME 3

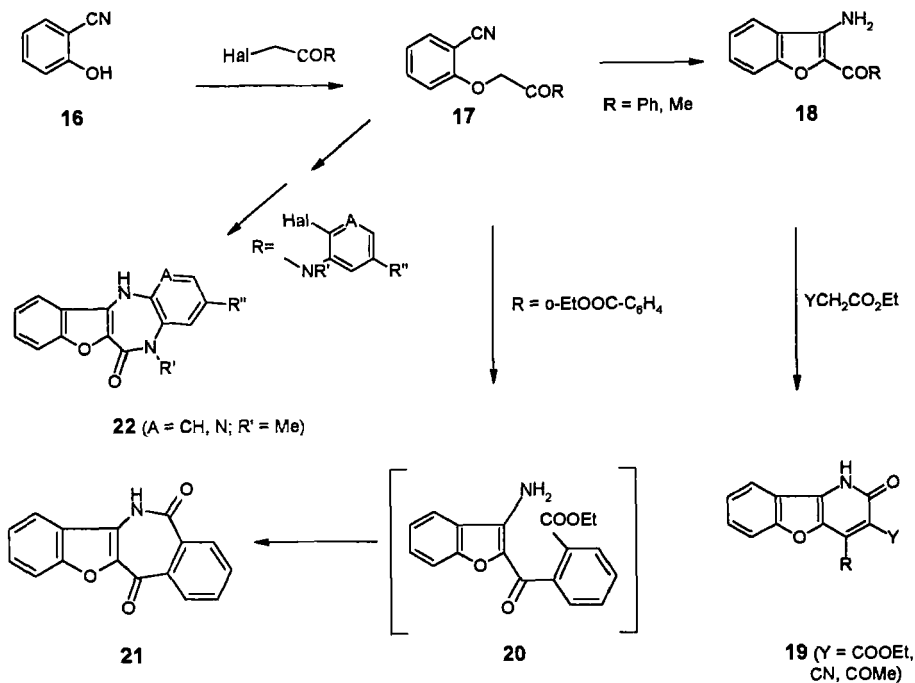


SCHEME 4

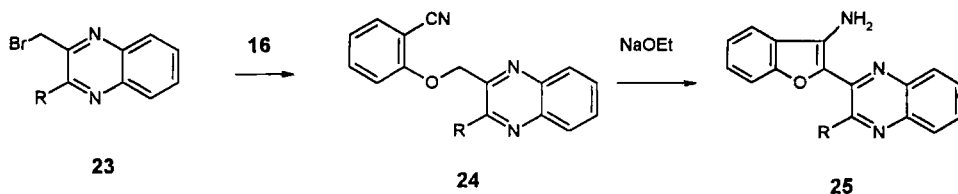
easily be obtained from corresponding acids and  $\alpha$ -haloketones (R = COAr, COMe).

### B. SYNTHESIS OF ANNULATED 3-AMINOFURANS

*o*-Cyanophenols are convenient starting compounds for the synthesis of 3-aminobenzofuran derivatives. Thus, *O*-alkylation of **16** followed by Thorpe-Ziegler cyclization of the intermediates **17** in the presence of  $\text{K}_2\text{CO}_3$  smoothly yields the 2-acyl-3-aminobenzofurans **18**, which are the starting compounds for the synthesis of benzofuro[3,2-*b*] pyridines (**19**) [81IJC(B)391] (Scheme 5).



SCHEME 5



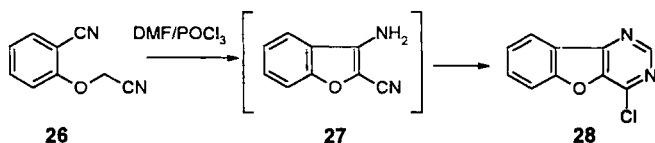
SCHEME 6

When ethyl *o*-bromoacetylbenzoate was used as an alkylating reagent in the presence of dimethylformamide (DMF) NaH, the expected Thorpe–Ziegler product (**20**) further cyclized to a condensed benzazepine-dione (**21**) (91JHC379) whereas benzofurobenzodiazepinones (**22**) were obtained with aromatic haloacetamides (90JHC1369) (Scheme 5). It was claimed that quinoxaline rings were sufficiently electron withdrawing to enable a Thorpe–Ziegler cyclization affording 3-amino-2-quinoxalinyln-benzofuranes (**25**) (91EGP292001) (Scheme 6).

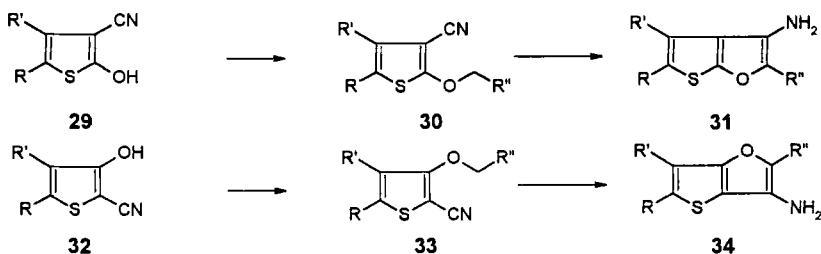
Interestingly, *o*-cyanomethoxybenzonitrile (**26**) gives a Thorpe–Ziegler type of cyclization under Vilsmeier conditions (DMF/POCl<sub>3</sub>), that is without the addition of a base. Further cyclization of the assumed 3-amino-2-cyanobenzofuran **27** with the Vilsmeier reagent afforded benzofuro-[3,2-*d*]pyrimidine (**28**) in poor yield, (91JHC263) (Scheme 7).

Thieno[2,3-*b*]furans (**31**) were obtained in modest yields (19–37%) starting from 2-hydroxy-3-cyanothiophenes (**29**) by *O*-alkylation with  $\alpha$ -bromoketones or bromoacetate via Thorpe–Ziegler cyclization of the resulting ethers (**30**) in the presence of NaOEt (83JPR457). High yields (50–95%) were achieved with isomeric 2-cyano-3-hydroxythiophenes (**32**), affording thieno[3,2-*b*]furans **34** (83JPR457) (Scheme 8). The authors (83JPR457) attribute this difference in reactivity to the higher electrophilicity of the cyano group in intermediates (**30**) as compared with **33**.

Furo[3,2-*b*]benzothiophenes (**37**) were synthesized in an analogous way (91JHC269) by smooth cyclization of the cyanomethyl ether **36** in the presence of K<sub>2</sub>CO<sub>3</sub>/DMF. The starting 2-cyano-3-hydroxybenzothiophene **35** was obtained from methyl 2-thiohydroxybenzoate and chloroacetonitrile. Under Vilsmeier conditions (POCl<sub>3</sub>/DMF), the 2-cyano-3-cyanomethoxy-



SCHEME 7

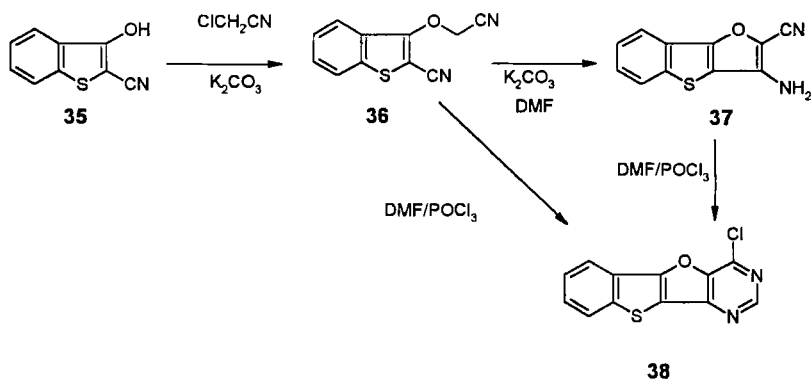


SCHEME 8

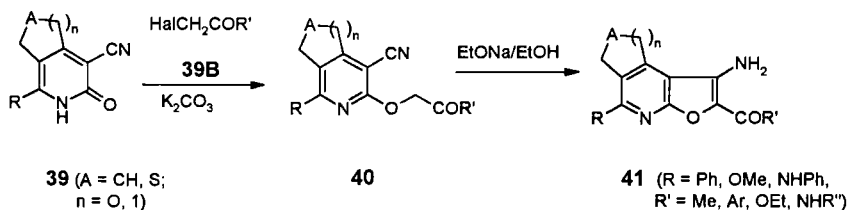
benzothiophene **36** also undergoes a Thorpe–Ziegler type of reaction, but further cyclization to the tetracyclic chloropyrimidine **38** was observed (91JHC269) (Scheme 9). The role that Vilsmeier conditions play in the mechanism of the Thorpe–Ziegler cyclization of **36** still remains unclear. Eventually intermediate 2-aza-3-chloro-propeniminium salts are formed by the addition of the formamide chloride to one of the cyano groups (88S655).

A great number of furo[2,3-*b*] pyridines were synthesized by *O*-alkylation of 3-cyano-pyridine-2-ones followed by base-catalyzed Thorpe–Ziegler cyclization of the resulting 2-alkoxy-3-cyanopyridines, which were often not isolated (82JPR933; 85MI2; 87IZV386; 89PS1; 92MI1; 95M945). For example, the interaction of condensed pyridine-2-ones (**39**) with halo carbonyl compounds followed by cyclization of **40** in the presence of EtONa afforded annulated aminofuopyridines (**41**) in high yields (82JPR933; 89PS1; 95M945) (Scheme 10). The latter can serve as starting materials for annulated pyrimidines (95M945).

The synthesis of the tetracyclic pyrido[3,2-*b*]furo [3,2-*b*]benzo[1,4]-diazepinone (**47**) starting with 2-cyano-3-hydroxypyridine (**42**) and 3-



SCHEME 9



SCHEME 10

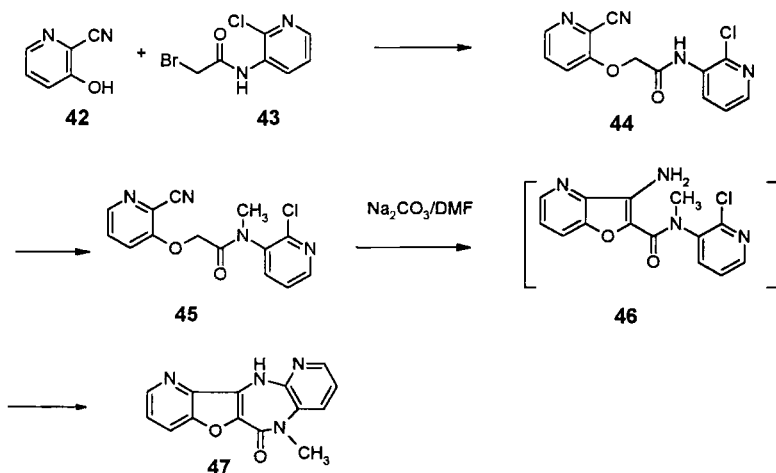
bromoacetylaminopyridine (**43**) also involves a Thorpe–Ziegler reaction, that is, formation of the aminofuropyridine **46**, which further forms a diazepine ring (Scheme 11). Because amide **44** resisted the base-catalyzed Thorpe–Ziegler cyclization, probably due to amide deprotonation, prior methylation of the amide was necessary (formation of **45**) (95H753).

Thorpe–Ziegler cyclization was further employed for the synthesis of aminofuro[2,3-*c*]pyridazine carboxylates (**50**) (90JPR104) and aminofurodibenz[*b,f*]azocines (**52**) (91KGS109) (Scheme 12).

### III. Synthesis of 3-Aminopyrroles

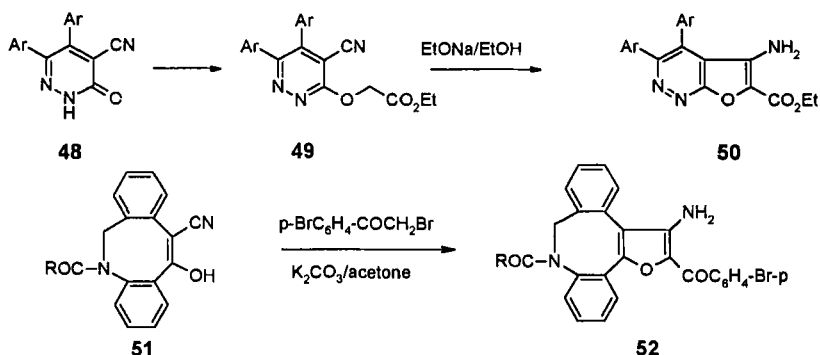
#### A. SYNTHESIS OF MONOCYCLIC 3-AMINOPYRROLES

Thorpe–Ziegler cyclization of CH-acidic 3-aminocrotonitriles (**54**) was frequently used in the synthesis of 3-aminopyrroles (**55**) (Scheme 13). Usually this pyrrole formation proceeds more easily than the synthe-



SCHEME 11

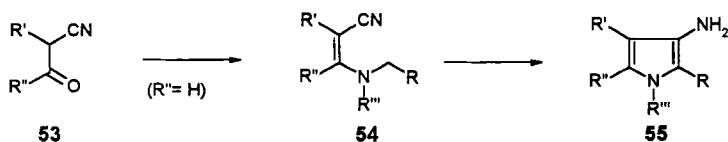




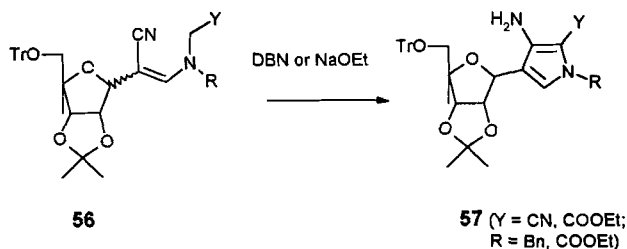
SCHEME 12

sis of analogous 3-aminofurane derivatives [see reference (86TL815)]. 3-Ethoxycarbonylmethylaminoacrylonitriles (**54**) ( $R'' = \text{COOEt}$ ), available from the corresponding  $\alpha$ -formylnitriles (**53**), afforded 3-aminopyrrole-2-carboxylates **55** ( $R'' = \text{COOEt}$ ) in the presence of NaOEt or *t*-BuOK, which could further be transformed into pyrrolo[3,2-*d*]pyrimidines (79JOC3826). The yields of **55** strongly depend on the substituent  $R'''$  attached to the nitrogen atom of **54**. Although secondary amino groups ( $R''' = \text{H}$ ) gave yields below 30%, better results (>90%) were achieved with tertiary amino groups ( $R''' = \text{alkyl}$ ) obtained by *N*-alkylation of **54** ( $R''' = \text{H}$ ) (Scheme 13). The authors explained this phenomenon by NH deprotonation when  $R''' = \text{H}$ , thus preventing the CH deprotonation necessary for a successful Thorpe–Ziegler reaction. The same effects were observed in the synthesis of pyrrolo[3,2-*d*]pyrimidine C nucleosides (**57**) in which benzyl ( $R = \text{Bn}$ ) (80TL1013) and ethoxycarbonyl ( $R = \text{COOEt}$ ) (81TL25; 83JOC780) were used as N-blocking groups (Scheme 14). Similar blocking of the enamine NH group was applied to the preparation of 4-alkyl, 4-alkenyl, and 4-pyridylmethyl 3-aminopyrroles (**59**) as potential immunosuppressants (91USP4985433, 91USP4985434) (Scheme 15).

Substitution of one of the two alkylthio-leaving groups of bis-alkylthioacrylonitriles (**60**) by aminoacid derivatives yielded substituted enamionitriles (**61**), which cyclized to 3-aminopyrroles (**62**) when heated in ethanol in the presence of triethylamine (88JPR1015) (Scheme 16).



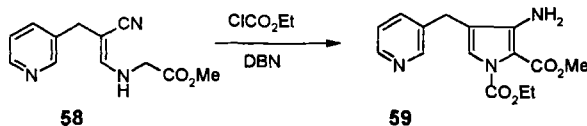
SCHEME 13



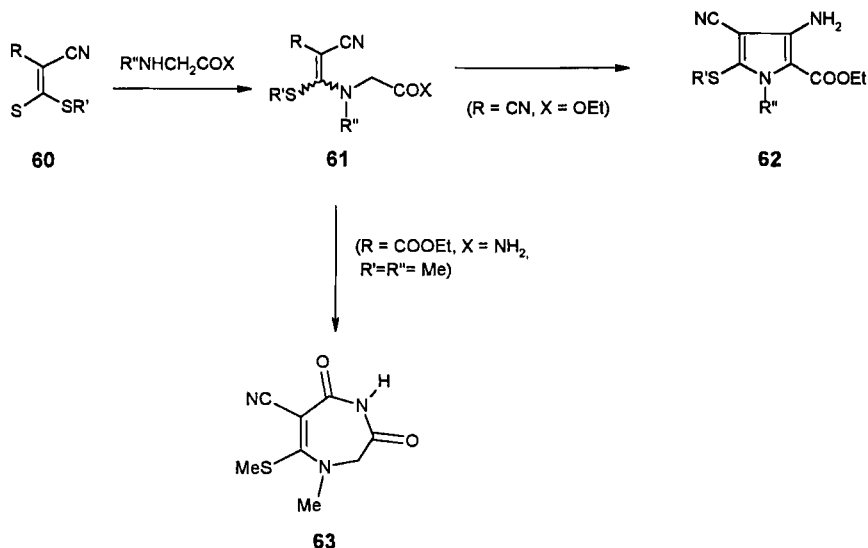
SCHEME 14

In contrast, the Thorpe-Ziegler cyclization failed with the glycine amide derivative **61** ( $X = \text{NH}_2$ ,  $R = \text{CN}$ ) (Scheme 16). In the opinion of the authors of the present review, this reluctance is likely caused by NH acidity rather than CH acidity as needed for Thorpe-Ziegler reactions. Interestingly, refluxing amide **61** ( $R' = \text{Me}$ ,  $X = \text{NH}_2$ ,  $R = \text{CO}_2\text{Et}$ ) in ethanol/ $\text{Et}_3\text{N}$  yielded the 1,4-diazepinedione **63** (88JPR1015). 3-Chloro and 3-ethoxyacrylonitriles (**64**) could be used as enaminonitrile precursors, directly affording 3-amino-pyrroles **65** in reactions with CH-acidic amines (93JPR491) in the presence of  $\text{AcONa}$  or  $\text{Et}_3\text{N}$  (Scheme 17). It is worth mentioning that the Thorpe-Ziegler cyclization to **65** proceeded smoothly even when  $R'$  was H (ie, no blocking of the NH acidity was necessary). Possibly, the high electrophilicity of the intermediate malonic acid derivatives (**67**;  $R = \text{electron withdrawing group}$ ) is responsible.

Another principal way to synthesize enaminonitriles (**67**) as precursors for Thorpe-Ziegler cyclizations to pyrroles (**65**) is the *N*-alkylation of enaminonitriles such as **66** (93JPR491). Intermediates **67** were isolated and cyclized to **65** in the presence of  $\text{NaOEt}$  (Scheme 17). When 2-cyano-3,3-diaminothioacrylanilide (**68**) was submitted to reactions with phenacyl bromides, the outcome depended on the conditions (Scheme 18). Triethylamine initiates an alkylation of the 3-amino group followed by Thorpe-Ziegler cyclization affording 2,4-diaminopyrroles **69**. In contrast, *S*-alkylation rather than *N*-alkylation took place when **68** reacted with phenacyl bromides in the presence of toluenesulfonic acid, leading to 1,4-thiazepines (**70**) (95JHC463, 95JHC1679) or to mixtures of **69** and **70**.



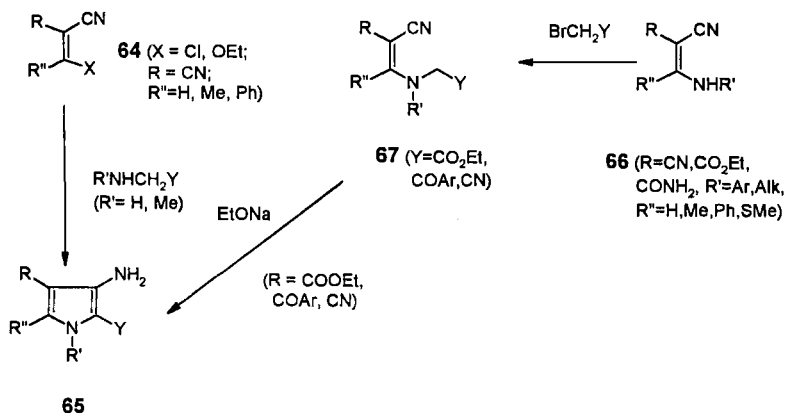
SCHEME 15



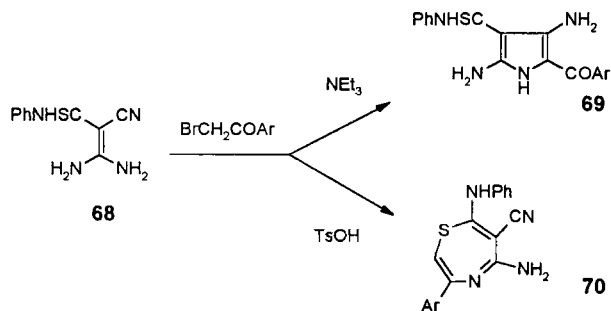
SCHEME 16

Interestingly, another type of cyclization occurred when 3-aminoacrylonitriles (**71**) were reacted with  $\alpha$ -haloketones in DMF/ $K_2CO_3$  (93JPR491). Alkylation of the 3-amino group was followed by substitution of the methylthio group by the carbonyl oxygen atom, affording oxazolines (**72**), which could also be ring transformed into Thorpe–Ziegler products **74** by ring opening (via **73**) in the presence of sodium alkoxides (Scheme 19).

3-Cyanomethylaminoenones or esters (**76**) (Scheme 20) can be consid-



SCHEME 17



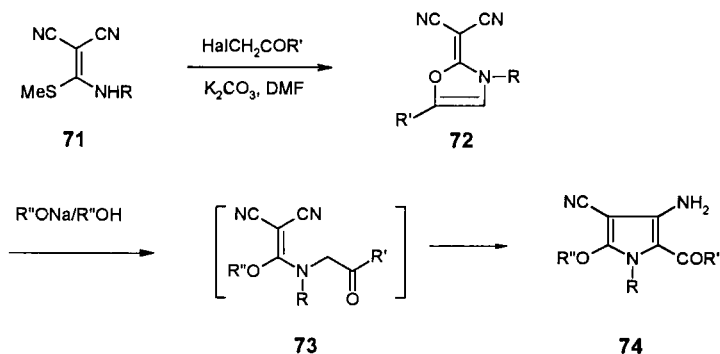
SCHEME 18

ered to be tautomers of precursors **1** ( $X = \text{CH}$ ,  $Y = \text{N}$ ,  $Z = \text{CHMe}$ ) for Thorpe–Ziegler cyclizations (see Scheme 1). They could be obtained from the corresponding 1,3-dicarbonyl compounds (**75**) and afford (via **77**) intermediate 3-aminopyrroles (**78**), which condensed to bisethoxycarbonylvinylamino-pyrroles (**79**) and then intramolecularly cyclized into pyrrolopyridines (**80**) (85JHC83;90JHC120) (Scheme 20).

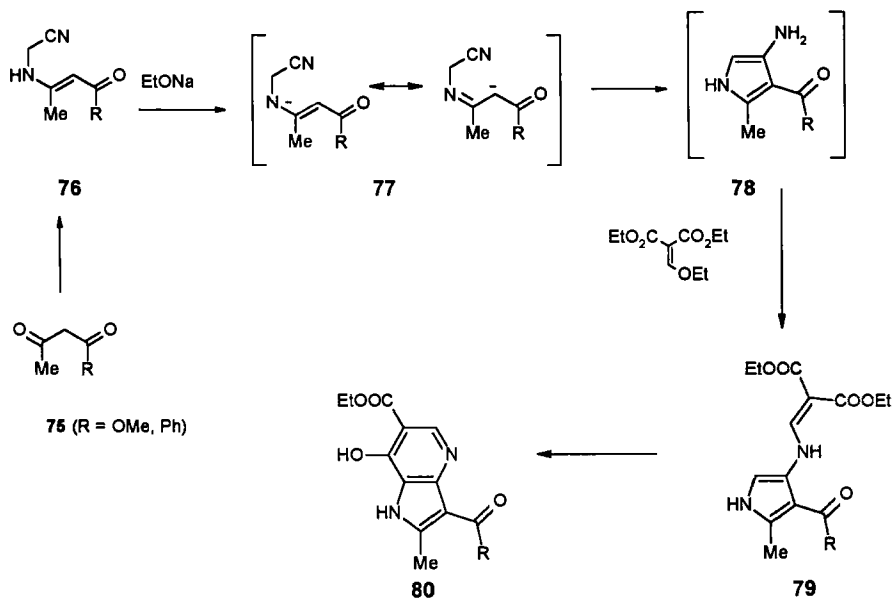
The formation of the 3H-3-morpholinopyrrole **82** from the cyanoazabutadiene **81** also involves a Thorpe–Ziegler type cyclization (Scheme 21) (for a further example in the tetrahydroindole series and the mechanism see Scheme 26) (87HCA187).

## B. SYNTHESIS OF ANNULATED 3-AMINOPYRROLES

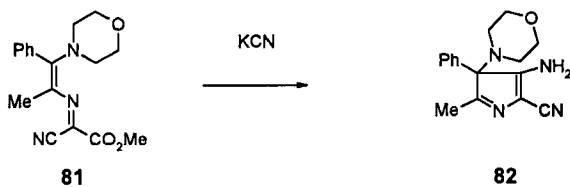
3-Aminopyrroles **85** (95HCA109) and **89** (93MC160; 96KFZ47) annulated with saturated carbocycles were synthesized from cyclic enaminonitriles **84** and **87** (formed from ketones **83**, **86**), respectively (Schemes 22, 23).



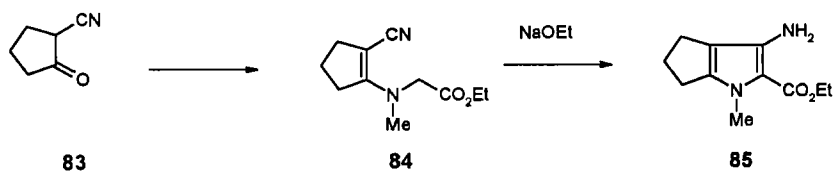
SCHEME 19



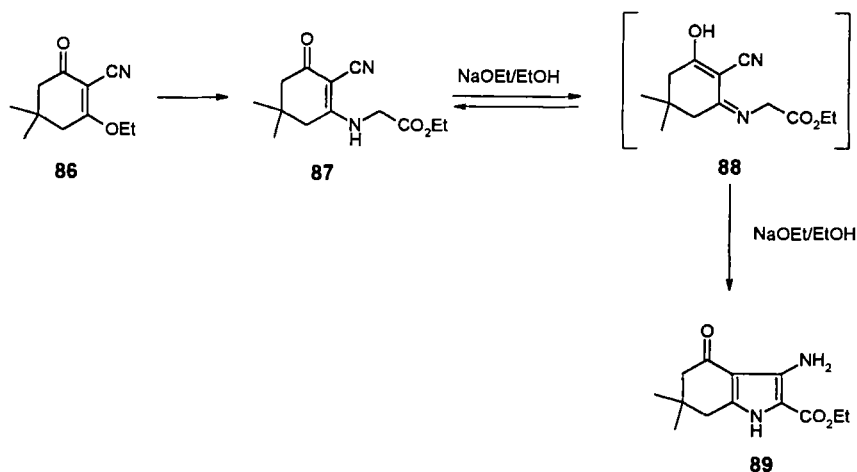
SCHEME 20



SCHEME 21

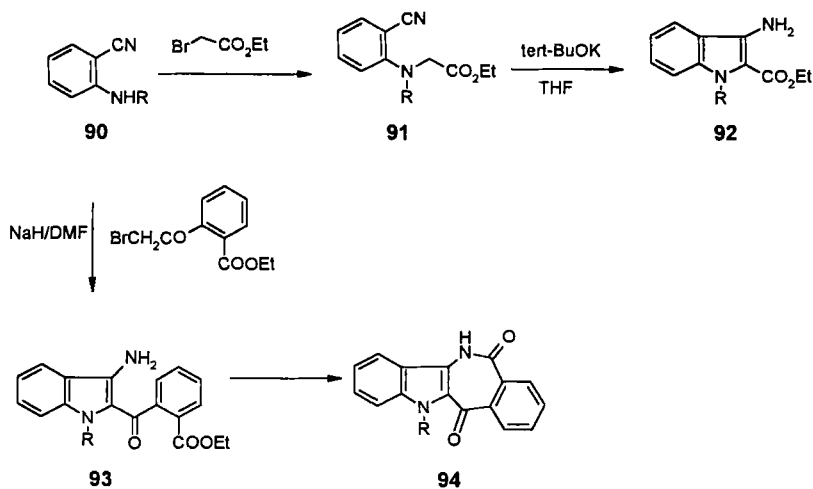


SCHEME 22

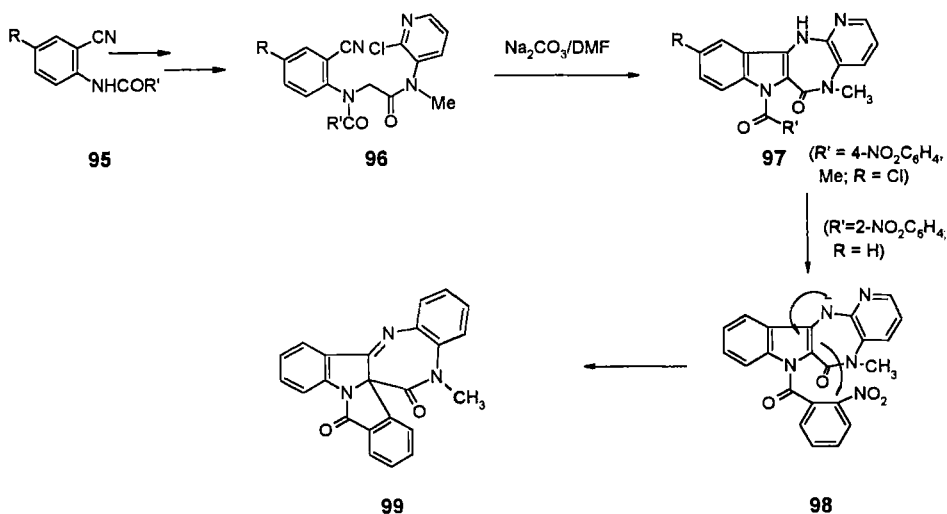


SCHEME 23

The smooth cyclization of the NH-acidic secondary enaminonitrile **87** was explained by intermediate rearrangement to the enol **88**, which is deprotonated at the  $\text{NCH}_2$  group, allowing Thorpe-Ziegler cyclization (96KFZ47) (Scheme 23). In the aromatic indole series such as **92** (83JHC495), precursors **91** for Thorpe-Ziegler cyclization were synthesized by alkylation of the corresponding *o*-aminobenzonitriles (**90**). Modest yields were achieved regardless of the degree of N-substitution ( $\text{R} = \text{H}$ : 50%;  $\text{R} = \text{Me}$ : 22%) (Scheme 24).



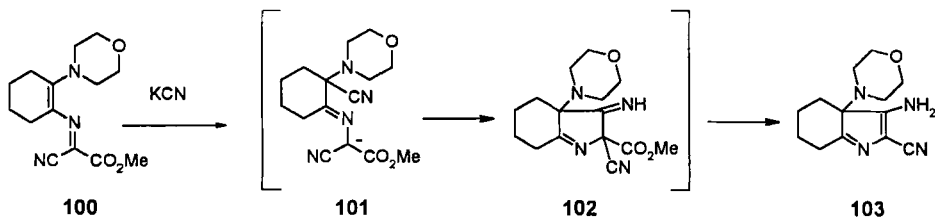
SCHEME 24



SCHEME 25

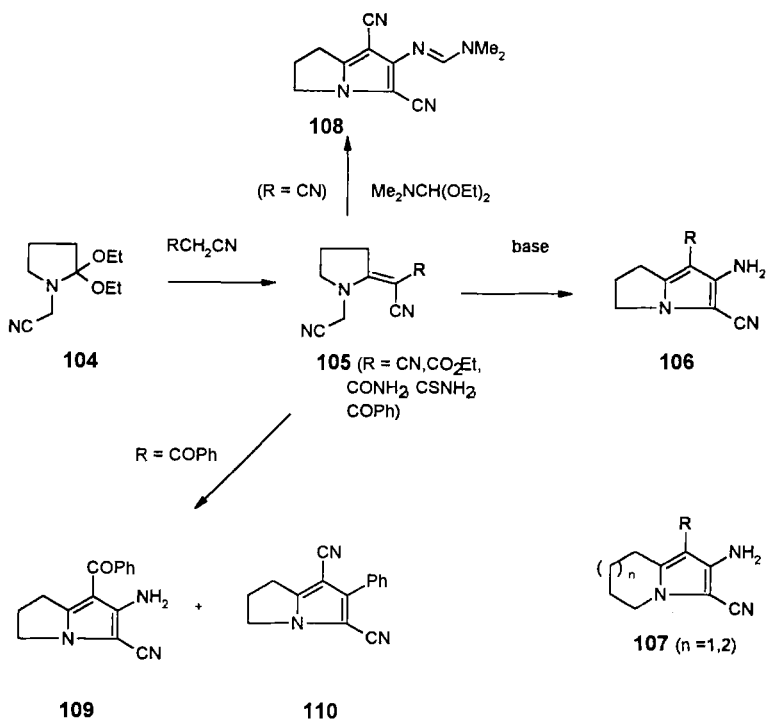
Thorpe–Ziegler synthesis of 3-aminoindoles with additional functional groups was used as part of the synthesis of condensed indoles [e.g., azepines (**94**) were obtained from 3-amino-2-benzoylindoles (**93**) (91JHC379) (Scheme 24)]. In these cases the nature of the substituent  $R$  is important for a smooth reaction ( $\text{Ac} < \text{Bz} < 2\text{-NO}_2\text{-benzoyl}$ , but no reaction when  $R = \text{H}$ ). With 2-chloro-3-( $N$ -bromoacetyl- $N$ -methylamino)pyridine and  $o$ -benzoylaminobenzonitriles (**95**), the condensed pyridodiazepinones **97** and **99** (95H753) were obtained via intermediates **96** and 3-aminoindoles intermediate (via **98**) 3-aminoindoles followed by substitution of the 2-chloro substituent by the resulting 3-amino group (Scheme 25).

Scheme 26 represents a special case of a Thorpe–Ziegler cyclization (87HCA187). Cyanide is added to 5-(dialkylamino)-2-aza-1,3-diene-1-carbonitrile (**100**), generating an anion, (**101**) that undergoes a Thorpe–Ziegler cyclization. The resulting product (**102**) cannot give a proton shift but loses the  $\text{COOMe}$  moiety to generate the amino group in the product **103**.



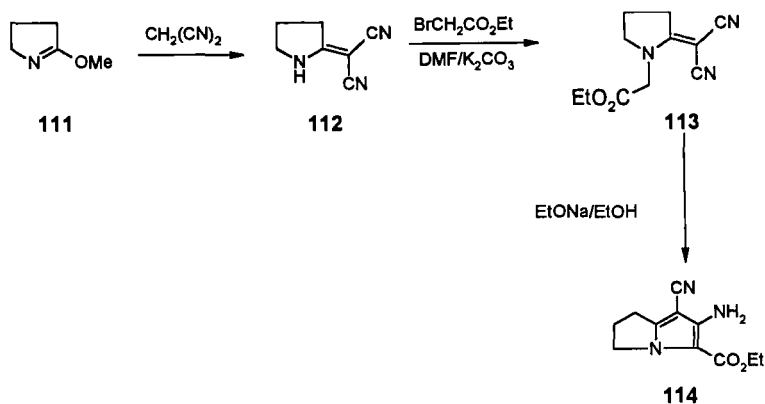
SCHEME 26

For other examples of the synthesis of annulated 3-aminoindole derivatives see Schäfer and Gewald (87JPR745). A number of investigations were allotted to the pyrrolizine synthesis by the Thorpe–Ziegler reaction. Thus, lactam acetal (**104**) could be condensed with acidic nitriles to give semi-cyclic enamino nitriles (**105**), which cyclized under basic conditions (e.g., 86KGS564; 87KGS1616; 87KFZ545, 90KFZ18; 91KFZ19, NaOEt), affording 3-amino-2-cyanopyrrolizines (**106**) (91KGS349; 94KFZ15) (Scheme 27). This method also was applied to the synthesis of pyrrolopyridines and pyrroloazepines (**107**) (94KFZ15) (Scheme 27). Thorpe–Ziegler reaction of enamino nitriles (**105**) was also possible in the presence of dimethylformamide diethylacetal, giving amidines (**108**) (87KGS1616) (Scheme 27). When  $\omega$ -cyanoacetophenone was condensed with the lactam acetal **104**, the corresponding enamino nitrile **105** (R = C(=O)Ph) was obtained as an *E/Z* mixture that cyclized to a 1:1 mixture of Thorpe–Ziegler product **109** and Dieckmann product **110** (91KFZ19) (Scheme 27).



SCHEME 27

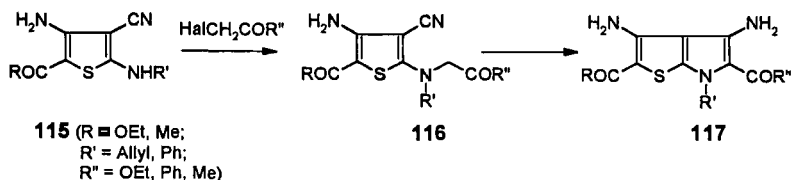




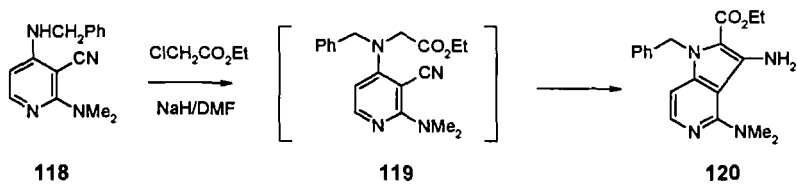
SCHEME 28

Another approach to the synthesis of pyrrolizines starts with the lactim ether **111**, which was condensed with malonodinitrile. The resulting enamino nitriles such as **112** were further *N*-alkylated with ethyl bromoacetate or phenacyl bromides, yielding intermediates such as **113**, which cyclize in the presence of NaOEt to the final products [e.g., **114** (90KFZ18; 91KFZ19) (Scheme 28)]. No intermediates were isolated when phase transfer catalysis was applied in the alkylation step. In a similar approach alkylation of an amino nitrile gave thieno[2,3-*b*]pyrroles (**117**) (Scheme 29) (86JPR459) and pyrrolo[3,2-*c*]pyridine (**120**) (Scheme 30) (95KFZ52) from 2-amino-3-cyanothiophenes (**115**) and the 4-amino-3-cyanopyridine **118**, respectively, and  $\alpha$ -halocarbonyl compounds (117 and 120 are obtained according to Schemes 115–116 and 118–119, respectively).

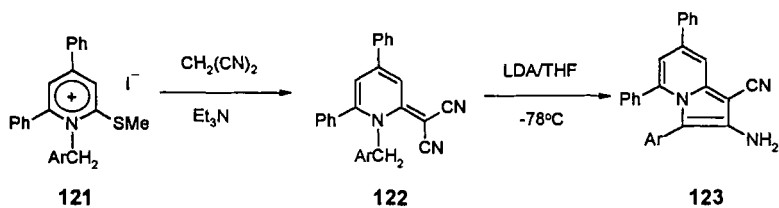
The synthesis of pyrrolo[1,2-*a*]pyridines (**123**) starting from 1-benzyl-2-methylthiopyridinium salts (**121**) could be achieved by replacement of the 2-methylthio group by malononitrile and Thorpe–Ziegler cyclization (Scheme 31) (85JHC113). The CH-acidifying effect of aryl substituents was sufficient for the ring closure when LDA was used as a base. When 2-cyanomethylidenepyridines (**124**), structural analogs of **122**, were submitted to Diels–Alder cycloaddition with *N*-phenylmaleinimide prior to Thorpe–



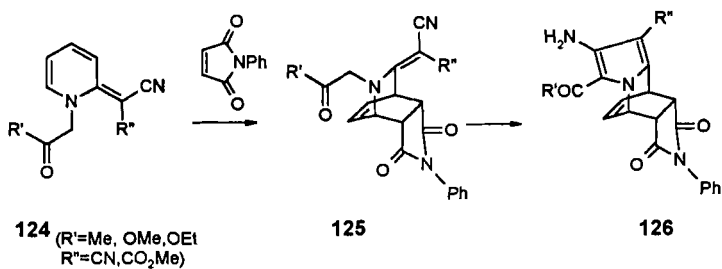
SCHEME 29



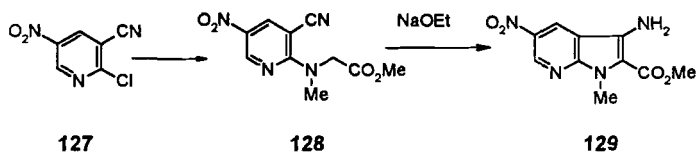
SCHEME 30



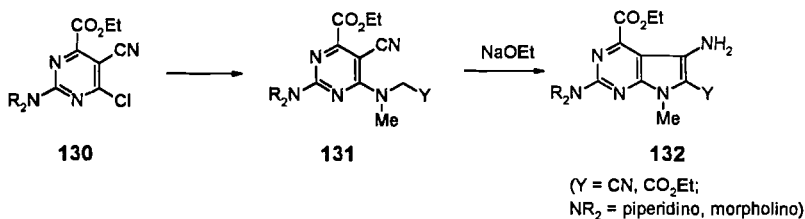
SCHEME 31



SCHEME 32



SCHEME 33



SCHEME 34

Ziegler cyclization, interesting polycyclic aminopyrroles (**126**) (via intermediate **125**) were obtained [89H51; 92H(33)195] (Scheme 32).

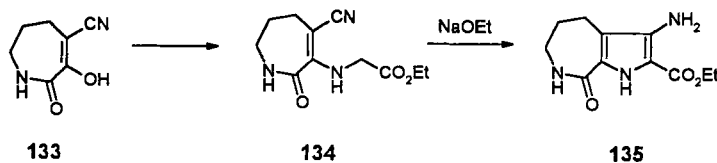
Substitution of chloride in *o*-chloronitriles **127** or **130** by glycine derivatives followed by Thorpe–Ziegler cyclization of the resulting *o*-aminonitrile structures was used to synthesize the 1-methyl-2-methoxycarbonyl-3-amino-5-nitro-pyrrolo[2,3-*b*]pyridine **129** (Scheme 33) (96KFZ36) and the pyrrolo[2,3-*d*]pyrimidines **132** (Scheme 34), (88LA633) respectively. Structural analogs of **128** with a hydrogen atom instead of a methyl group resisted cyclization. In spite of the presence of two acidic NH hydrogen atoms 3-amino-4-cyano-azepinone **134** underwent Thorpe–Ziegler cyclization to the pyrroloazepine **135** (80KGS109781TH1) (Scheme 35).

## IV. Synthesis of 3-Aminothiophenes

There are numerous applications of the Thorpe–Ziegler reaction for the synthesis of thiophenes and annulated thiophenes. Only selected examples can be covered here. For more examples see reviews (85MI1; 86MI1; 92MI1).

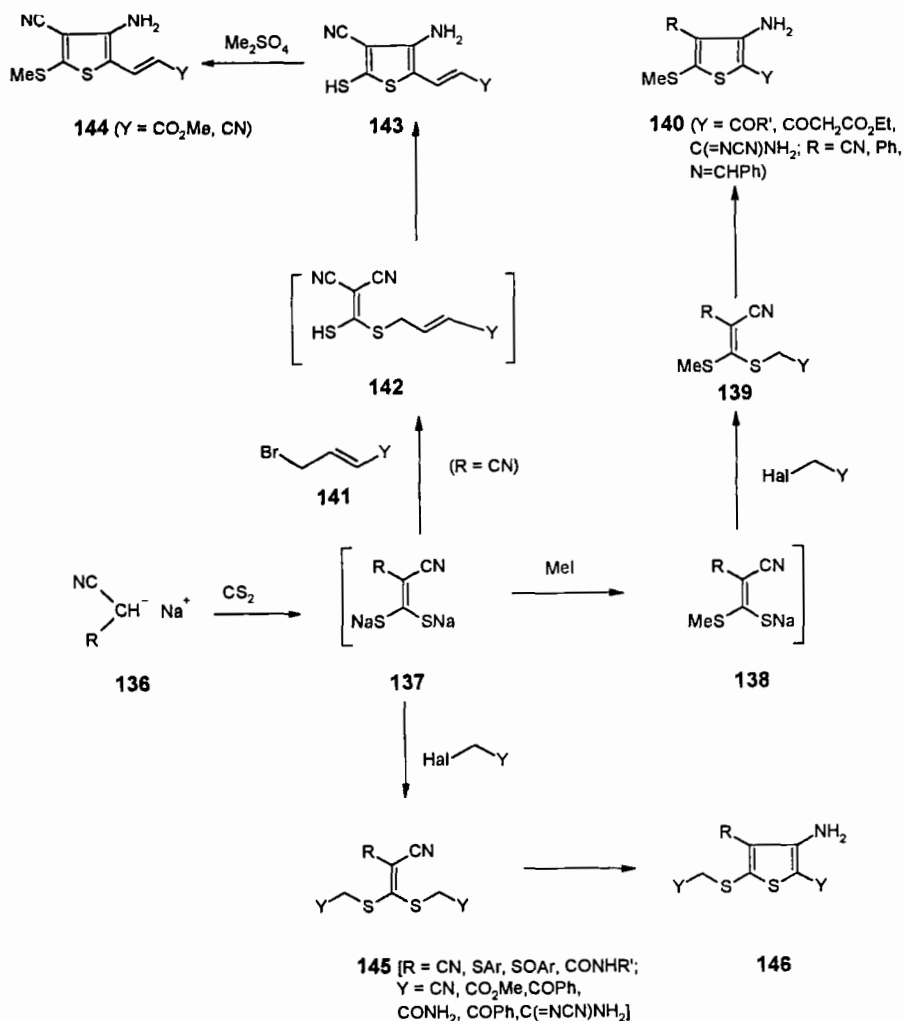
### A. SYNTHESIS OF MONOCYCLIC 3-AMINOTHIOPHENES

Ketene dithiolates (**137**), readily available from the corresponding substituted acetonitriles and carbon disulfide, serve as versatile starting materials for the synthesis of monocyclic 3-aminothiophenes (Scheme 36). Thus, one sulfur atom was methylated (formation of **138**); the other was alkylated



SCHEME 35

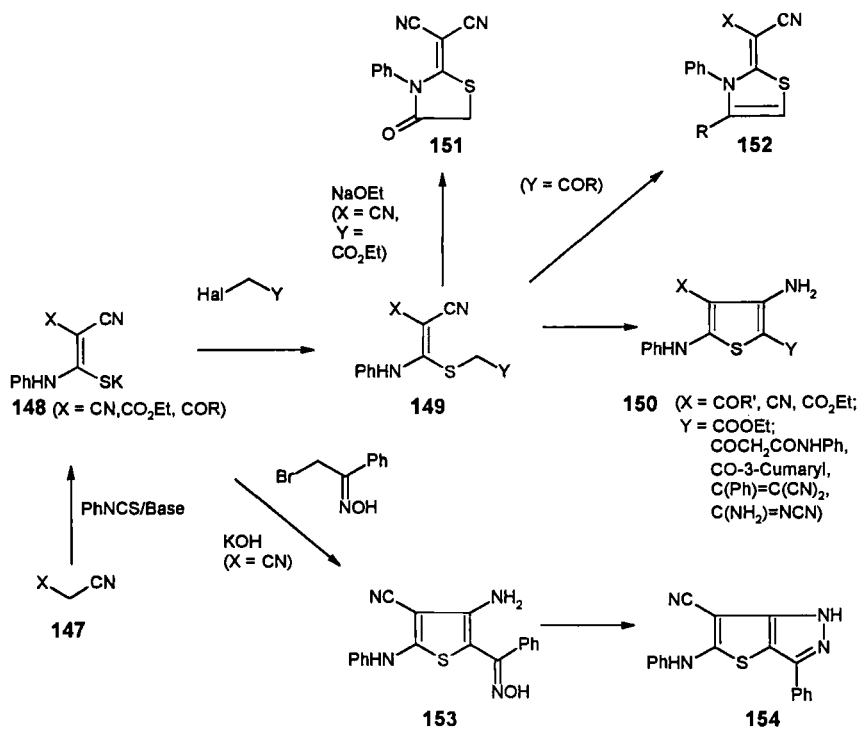
with a CH-acidic alkyl halide to **139**, allowing Thorpe–Ziegler cyclization to 3-amino-5-methylthiophenes (**140**) (83CPB2480; 84EGP206993, 84H697; 96T1011). The alkylation sequence could also be changed, that is, first introduction of the acidic alkyl substituent (with usage of **141**—formation of **142**) followed by Thorpe–Ziegler reaction to 3-amino-5-thiohydroxythiophenes (**143**) and final *S*-methylation, giving **144** (Scheme 36) (90LA115). Furthermore, both sulfur atoms of ketene dithiolates (**137**) could be *S*-alkylated by



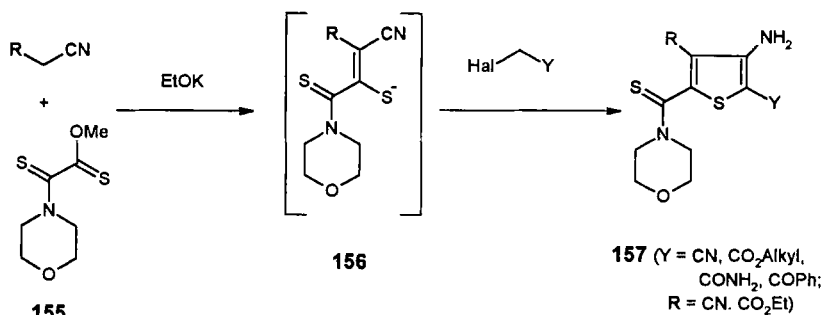
SCHEME 36

CH-acidic alkylating reagents, affording ketene dithioacetals (**145**), which underwent Thorpe–Ziegler cyclization to 3-aminothiophenes (**146**) (85BCJ2441; 86BCJ338; 89EGP265625; 92LA395; 94JHC771; 96T1011) (Scheme 36) or thieno[2,3-*b*]thiophenes (**176**) by twofold Thorpe–Ziegler cyclizations (see Section IV.B, Scheme 44).

Keten-*S,N*-acetals **148**, derived from the addition of acidic nitriles (**147**) to phenyl isothiocyanate [for an *in situ* method, see Mohareb (92M341)], were used for the synthesis of 2,4-diaminothiophenes such as **150** via the Thorpe–Ziegler reaction (Scheme 37) [86MI2; 91AP469; 92JCR(S)154; 92M341, 92MI2; 95ZOR127]. With  $\alpha$ -haloketones or  $\alpha$ -bromoesters an alternative cyclization was observed: Nucleophilic attack of the anilino substituent at the carbonyl group of the intermediate alkylation product **149** led to 1,3-thiazolidine-4-ones (**151**) (91AP469) or 1,3-thiazolines (**152**) (Scheme 37) [91AP469; 92JCR(S)154]. In some cases this problem could be circumvented by using  $\alpha$ -bromooximes rather than ketones, affording corresponding oximes (**153**) of 2-benzoyl-3-aminothiophenes. The oximes (**153**) could be submitted to an interesting cyclocondensation to thienopy-



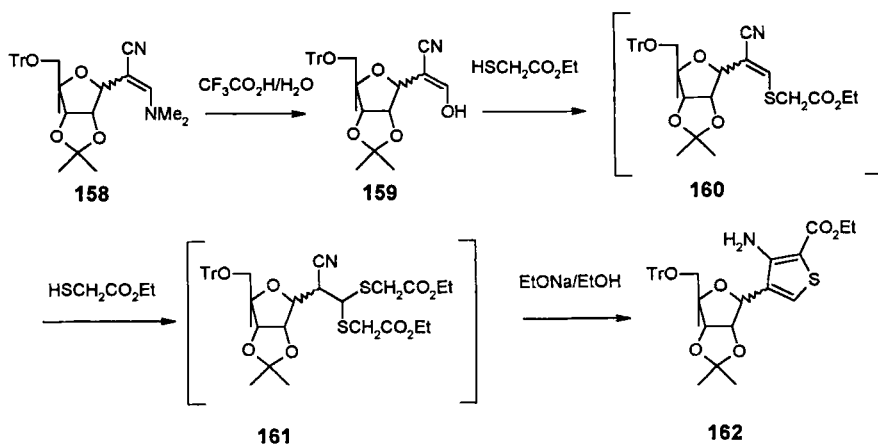
SCHEME 37



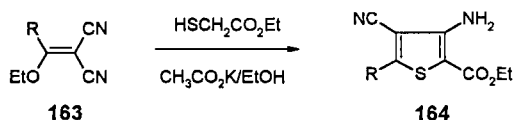
SCHEME 38

razoles (**154**) (91AP469) (Scheme 37). The dithiooxalester amide **155** was used to generate the 3-thiohydroxyacrylonitrile **156** by condensation, allowing the synthesis of 3-aminothiophenes (**157**) with a thioamide function in position 5 (87AP43) (Scheme 38).

Substituted 3-dimethylamino (**158**) and 3-alkylthioacrylonitriles (**160**) used as precursors for Thorpe–Ziegler cyclization to 3-aminothiophenes such as **162** (Scheme 39) (82JOC4633), **164** (Scheme 40) (82S1056), and **167** (Scheme 41) (84S275; 87PS351; 92M455) were obtained by substitution reactions with  $\text{CH}_3\text{-acidic methyl thiols}$  in which  $\text{OH}$  (**159**),  $\text{EtO}$  (**163**), or chloride (**165**) served as leaving groups in the starting acrylonitriles. The addition of a second molecule of thioglycolate (formation of **161**) in the course of the formation of the C-nucleoside **162** also took place (82JOC4633). The transforma-



SCHEME 39



SCHEME 40

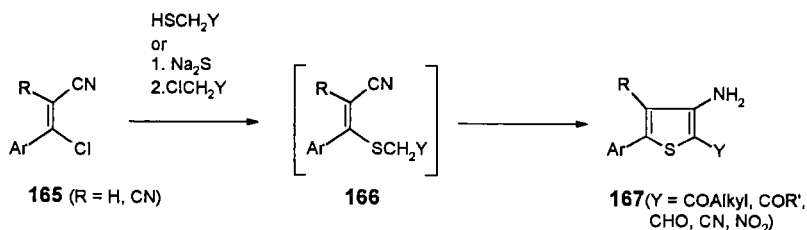
tion of 3-chlorocinnamonnitriles (**165**) into 3-aminothiophenes (**167**) could alternatively be achieved by primary substitution of chloride by sulfide followed by *S*-alkylation and cyclization (92M455) (Scheme 41).

In addition to  $\beta$ -chloroacrylonitriles (**165**),  $\alpha$ -chloroacrylonitriles (**168**) were used as starting material to make 3-aminothiophenes (**170**) (Scheme 42) [83JPR876; 89EUP298543; 92JAP(K)06/117, 263; 93JCR(S)(2)72]. Intermediates **169** could be isolated and cyclized in a separate step (89EUP298543; 93JCR(S)(2)72; 94JAP(K)06, 25, 221). Furthermore, 2,3-dihalonitriles (**171**) were claimed to be starting materials for the preparation of 3-aminothiophenes (**170**) [92JAP(K)06/117, 263] (Scheme 42).

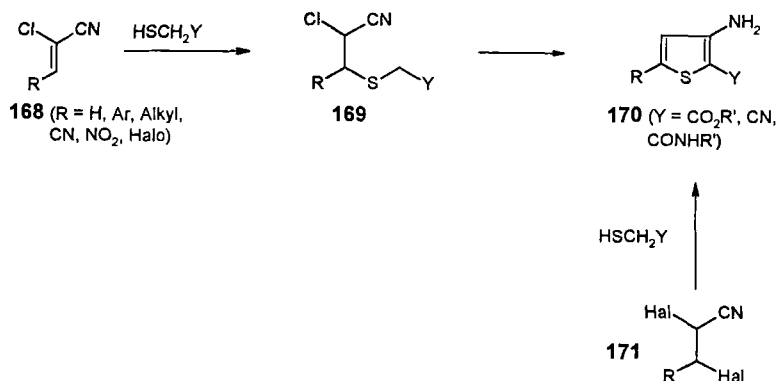
Finally, cyanoalkynes (**172**) also were used as precursors for 3-aminothiophenes (86JHC1757). Presumably, this synthesis starts with the addition of cyanomethylthiolate, affording intermediate  $\beta$ -cyanomethylthioacrylonitriles similar to **166** that finally undergo Thorpe–Ziegler cyclization to **173** (Scheme 43).

## B. SYNTHESIS OF ANNULATED 3-AMINOTHIOPHENES

The synthetic approach to 3-aminothiophenes starting from ketene dithiolate (**174**  $\rightarrow$  **175**) followed by Thorpe–Ziegler cyclization described in the previous section (see Scheme 36), was also applied to the synthesis of thieno[2,3-*b*]thiophenes (**176**) [Y = COR (85BCJ2441; 87MI2; 92PS15), CN (92PS15), CO<sub>2</sub>Et (92PS15) CH=CHCN (90LA115), CH=CHCOOMe (90LA115), C(NH<sub>2</sub>)=NCN (96T1011)] (Scheme 44). Two equivalents of



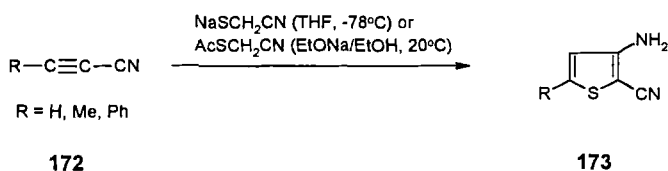
SCHEME 41



SCHEME 42

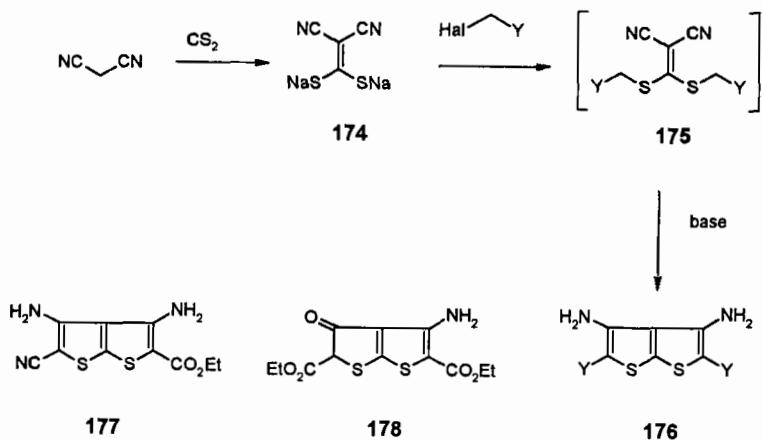
the CH-acidic alkylating reagent had to be used. By applying phase transfer catalysis and stepwise addition of different alkylating reagents, the asymmetrically substituted product **177** was obtained (92PS15) (Scheme 44). When ethyl cyanoacetate was used in place of malonodinitrile, Thorpe–Ziegler cyclization and Dieckmann cyclizations occurred after reaction with two equivalents of ethyl chloroacetate, affording mixtures of thieno[2,3-*b*]thiophenes **177** and **178** (92PS15).

In the synthesis of thieno[3,2-*d*]-1,2-thiazoles (**182**) (Scheme 45) (82AJC393), thieno[2,3-*d*]-1,3-dithioles (**186**) (Scheme 46) (87S655), and thienoazaindolizines (**189**) (Scheme 47) (90CPB2667) another strategy was applied: first preparation of a heterocycle bearing an *o*-thiohydroxynitrile or *o*-methylthiohydroxynitrile group and then formation of the thiophene ring by Thorpe–Ziegler cyclization. Thienoindolizines (**192**) (via **190**, **191**) could be obtained in a similar way (Scheme 48), but due to the presence of two electrophilic groups ( $R' = CN, R^1CO, CO_2Et$ ) in positions 1 and 3 of the starting indolizine, a selectivity problem appeared. Thorpe–Ziegler cyclization or Dieckmann condensation could occur by way of these positions [87CL2043; 89BCJ119; 90CPB1527; 91JAP(K)03, 99081; 92CPB2313]. Based on quantum chemical calculations (89BCJ119; 92CPB2313) and ex-



SCHEME 43

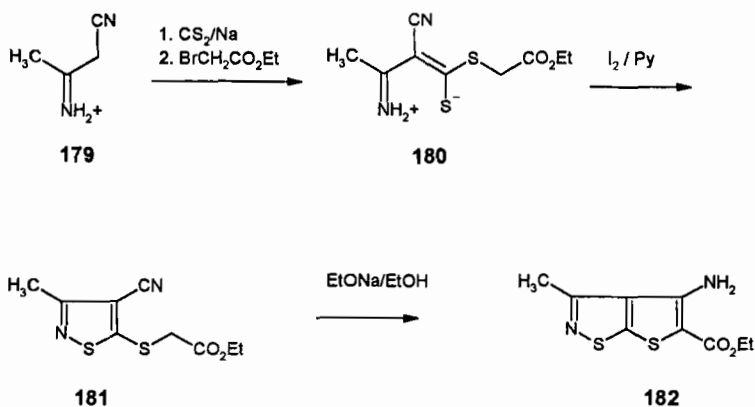




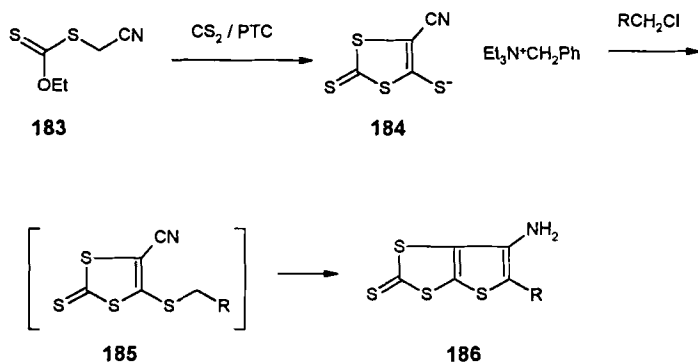
SCHEME 44

perimental data (87CL2043; 89BCJ119; 90CPB1527; 92CPB2313), the following order of reactivity of substituents in the desired Thorpe–Ziegler cyclization was determined: 3-CN > 1-CN > 3-keto > 3-ester > 1-ester. Thus, the substitution pattern shown in Scheme 48 gave unambiguously the Thorpe–Ziegler cyclization products **192**.

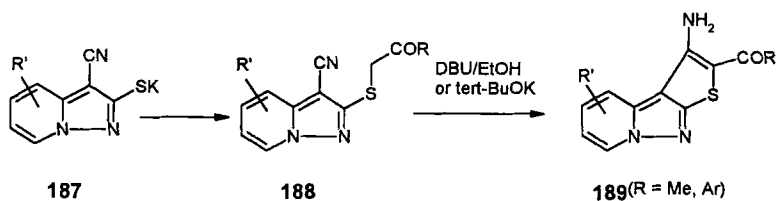
Alternatively, the acidic methylthio group was introduced by substitution of a suitable leaving group (Oalkyl, SMe, Halo, NO<sub>2</sub>) in a cyanoheterocycle or cyanocarbocycle to obtain precursors for Thorpe–Ziegler cyclizations. In this way pyrrolo[4,3-*b*]thiophenes (**195**) (via **193**, **194**) (Scheme 49) (88S449),



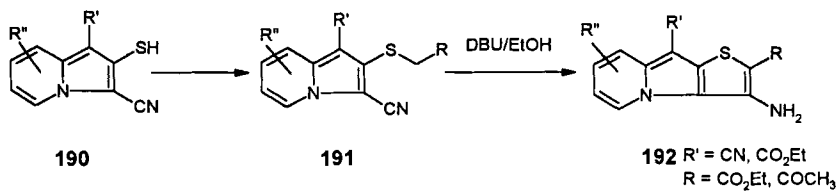
SCHEME 45



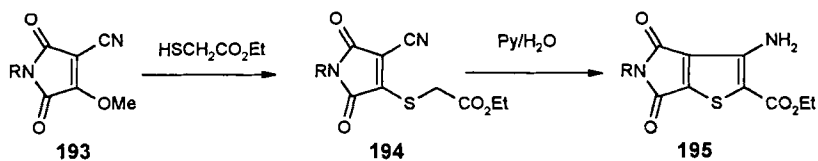
SCHEME 46



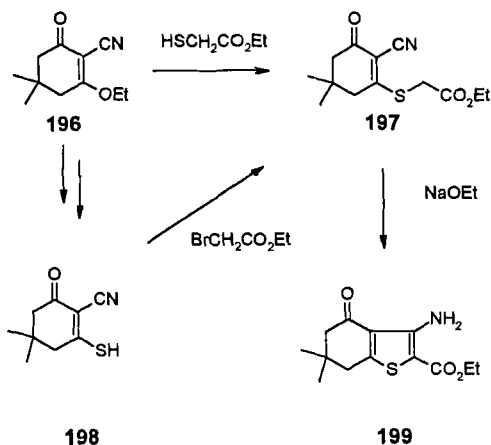
SCHEME 47



SCHEME 48

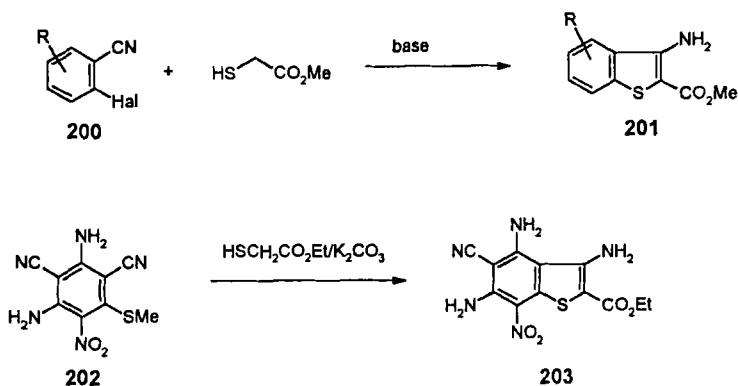


SCHEME 49

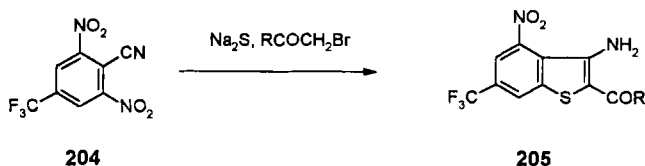


SCHEME 50

tetrahydrobenzo[*b*]thiophenes (**199**) (via **196–198**) (Scheme 50) (93MCI60), and benzo[*b*]thiophenes [**201** (via **200**) (Scheme 51) (80JHC1399; 92JMC2712) and **203** (from **202**) (Scheme 51) (85JPR328)] were obtained using thioglycolates as nucleophiles. This strategy was also followed in a stepwise way, first by thiolysis and subsequently by *S*-alkylation to synthesize the benzo[*b*]thiophenes (**205**) (from **204**) (95MI1) (Scheme 52). In the syntheses of 3-aminobenzo[*b*]thiophenes **210** (via **207, 208**) (Scheme 53) (81ZC183) and **213** (Scheme 54) (80LA768), precursors **209** and **212** were generated by Dimroth rearrangement of 2-aminothiopyranes (**206**) or by nucleophilic ring opening of benzoisothiazoles (**211**) respectively.



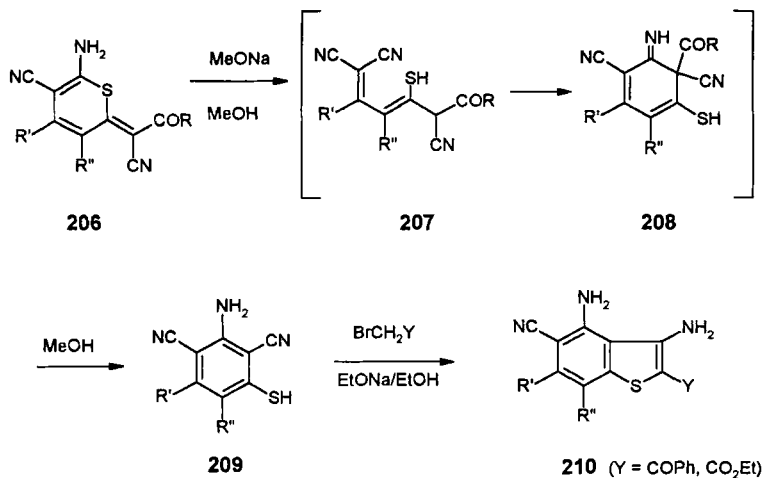
SCHEME 51



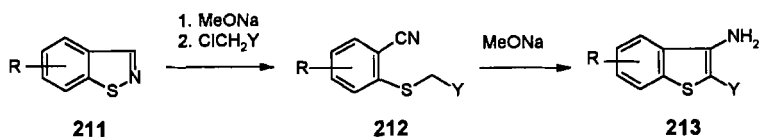
SCHEME 52

The formation of 3-amino-2-nitrobenzothiophene (**217**) (from **214**) by reaction of *o*-thiohydroxybenzonitrile and bromonitromethane looks like a normal Thorpe–Ziegler reaction [83JCS(CC)834; 86JCS(P1)1171] (Scheme 55). However, investigations of the mechanism revealed the formation of intermediate disulfides (**215**) rather than the expected *S*-alkylation products (**218**). The former are attacked at the cyano group by the nitromethane anion and close the thiophene ring by intramolecular disulfide cleavage (via **216**) [86JCS(P1)1171].

Thorpe–Ziegler cyclization is the most important route to thieno-[2,3-*b*]pyridines (**221**) (85MI1; 86MI1; 92MI1) (Scheme 56). Conveniently, the corresponding precursors (**220**) were obtained from pyridine-2-thiones (**219**) by *S*-alkylation in the presence of bases [89PS1; 92JCR(S)144; 95H753; 96KFZ36, 96T1011]. This approach has been widely used for the synthesis of numerous 3-cyanopyridine-2-thiones having alkyl and aryl substituents [86PHA827; 88KGS805; 89SUL47; 90MI2; 91PHA51, 91ZOB942; 92JPR483, 92KGS1280, 92PHA11; 93AP959, 93CCC1931, 93DOK97, 93JCR(S)(7)256, 93MI1, 93MC149; 96KGS59, 96KGS115], bearing func-

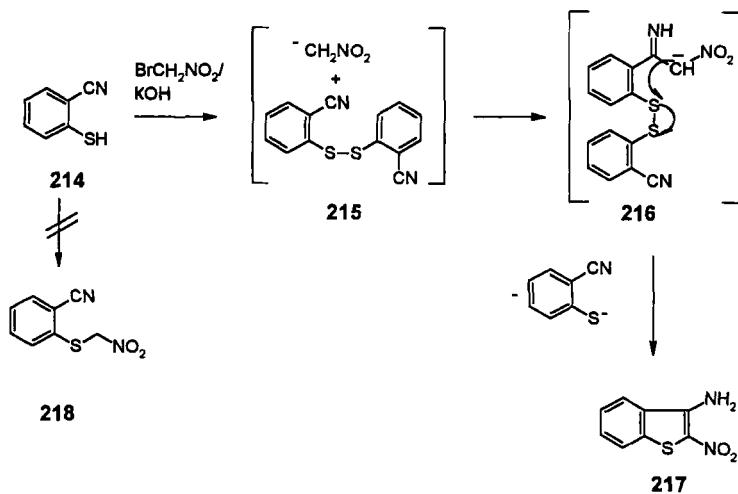


SCHEME 53

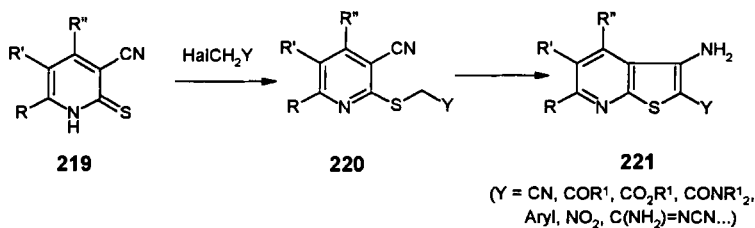


SCHEME 54

tional groups [89PS95; 90EGP275688, 90ZOB2384, 90ZOB2750; 91AP853, 91IZV1643, 91JCR(S)178, 91SL27, 91ZOB942; 92H(34)1721, 92JHC1693, 92KFZ62, 92MI3; 93BCJ555, 93LA1003; 94JCS(P1)1449, 94T6705, 94ZOR581], and being annulated to carbo- and heterocycles [85ZOB1656; 86ZOR1291; 88ZOR460; 89CS327; 91CCC1749, 91JCR(S)(5)116, 91PS(57)293, 91ZOR1996; 92BCJ2241; 93BCJ3716; 94KGS122; 95KGS250; 96KGS512], and for the synthesis of 3-cyano-1,4-dihydropyridine-2-thiones (87KGS124; 92KFZ40; 96KGS553). As shown in the 6-(pyrid-3-yl)-pyridine series (**222**) (Scheme 57) the ease of the cyclization step correlates with the chemical shift of the CH<sub>2</sub> protons of the precursor **220** in the <sup>1</sup>H NMR spectra and depends on the type of electron-withdrawing substituent Y (Y = CPh, CN, CO<sub>2</sub>Et, CONR<sub>2</sub>, COOH) (88KGS805). Appropriate reaction conditions were determined for different Y groups to match the CH acidity in these precursors. Thus, COOEt-substituted precursor **220** was found to be more reactive (MeONa as base) than the corresponding 4-nitrophenyl or 4-cyanophenyl derivatives (*t*-BuOK as base) in the formation of the thienopyridines (**223**; Y = CO<sub>2</sub>Et, 4-C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, 4-C<sub>6</sub>H<sub>4</sub>CN) [91JCR(S)(7)178] (Scheme 57).



SCHEME 55

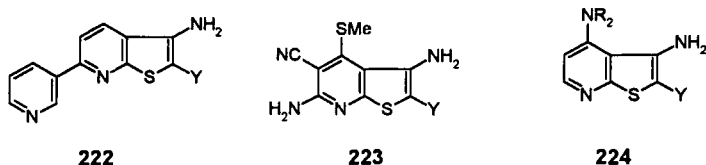


SCHEME 56

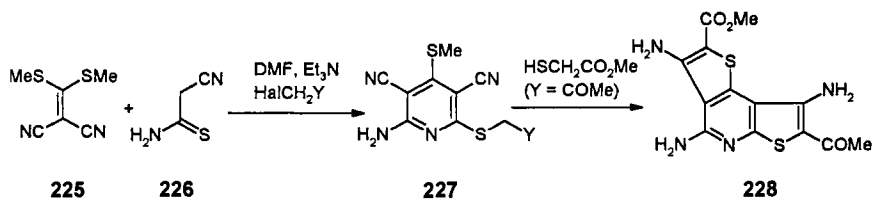
Other substituents in the precursors **220** may also influence the cyclization tendency to thienopyridines (**221**) (93MC149) (Scheme 56). Thus, an intermediate (**220**) could be isolated during the synthesis of diaminothieno[2,3-*b*]pyridines (**224**) ( $\text{Y} = \text{CONR}^1_2$ ) when  $\text{NR}_2$  was  $\text{NMe}_2$ , whereas the corresponding less electron-donating anilino derivative ( $\text{NR}^1_2 = \text{NHPh}$ ) immediately cyclized (92KFZ62) (Scheme 56). In addition to the transformation to thienopyridines (**221**) the 2,4-bisalkylthiopyridines (**227**) (formed from **225**, **226**) also allowed the annulation of a second thiophene ring by the Thorpe–Ziegler reaction, affording the bithienopyridine **228** [92JCR(S)144] (Scheme 58).

The formation of tetracyclic thiophene (**232**) (via **231**) by the Thorpe–Ziegler reaction in the presence of *N*-bromosuccinimide (NBS) represents a special case, because the pyrimidine-2-thione **229** also served as precursor for the CH-acidic alkylation agent **230** (95H2195) (Scheme 59).

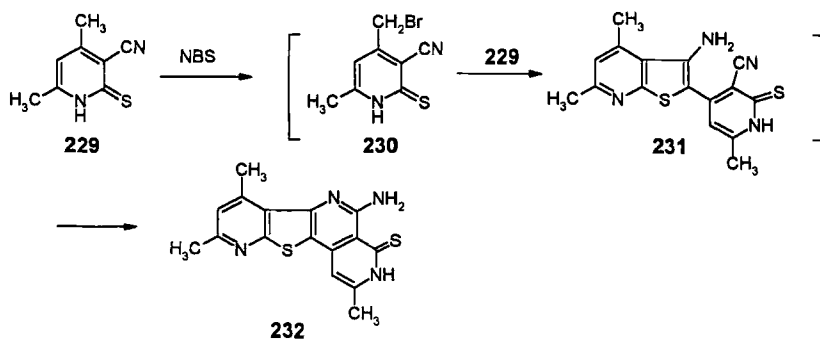
The aminothiophene synthesis by the Thorpe–Ziegler cyclization (Scheme 53) could also be applied to the preparation of thienoquinolines (**234**) (from **233**) [86JHC925; 88JCR(S)50; 92CCC2359, 92PS219; 95SC451] and thienoisquinolines (**235**) (84ZOR2442) (Scheme 60). The formation of *N*-substituted thieno[2,3-*b*]pyridines such as **237** were reported to be the result of the reaction of dimeric malodinitrile (**236**) with phenyl isothiocyanate and alkylating reagents such as ethyl chloroacetate (92M341) (Scheme 61). Similarly, by the formation of both a six-membered ring and a thiophene ring, the benzo-annulated *N*-substituted thienopyridinone **240** (91EUP416820), and the thienobenzodithiines **243** (84S854) were synthesized starting from methyl *o*-cyanomethylbenzoate (**238**) or the *o*-chlorophenylsulfone **241** (via **239**, **242**), respectively (Scheme 61).



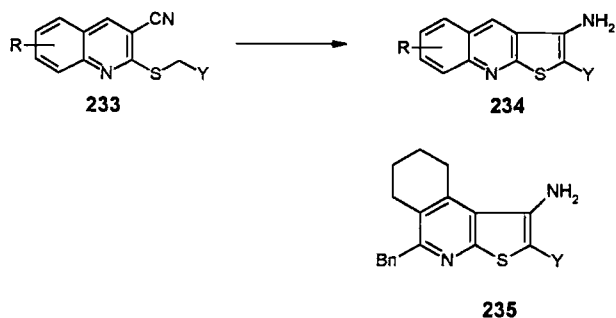
SCHEME 57



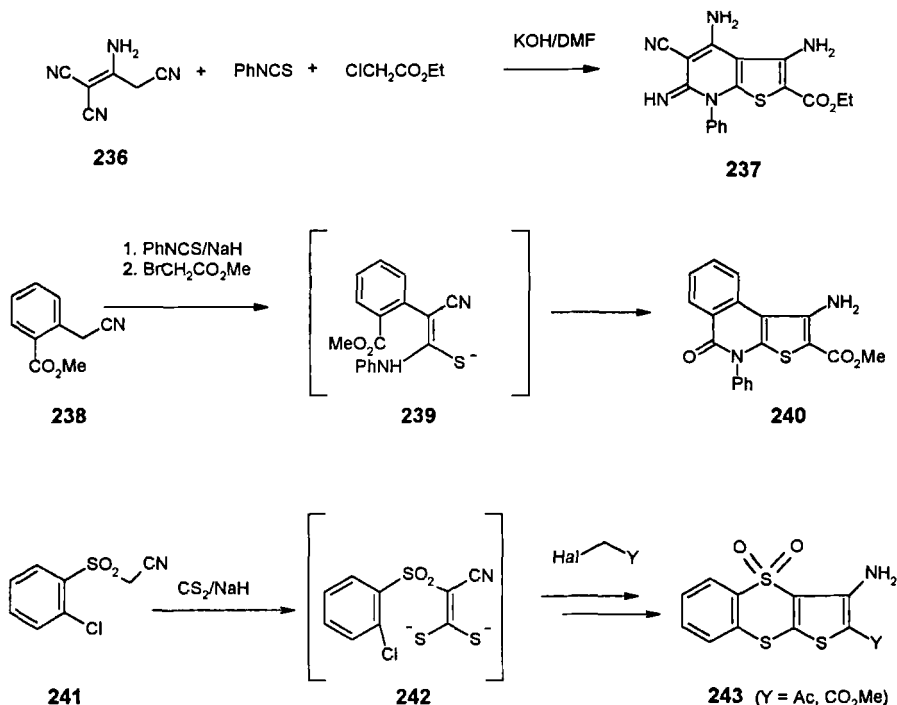
SCHEME 58



SCHEME 59



SCHEME 60

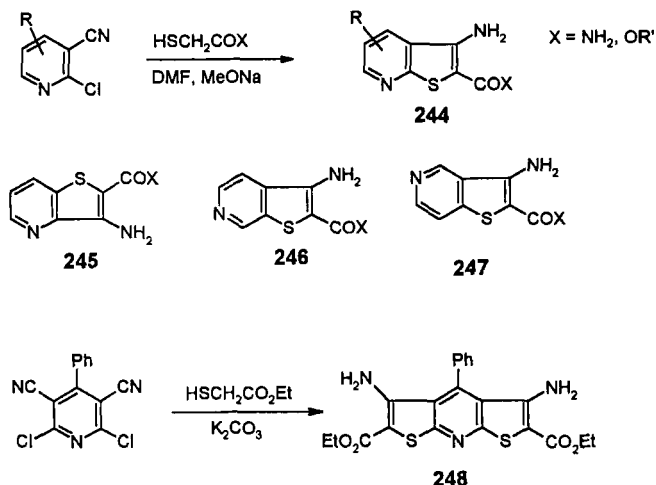


SCHEME 61

Another important route to thienopyridines with general structure **244** is based on the reaction of *o*-chlorocyanopyridines with thioglycolates [87JHC85; 91PHA415; 92IJC(B)492, 92JOC4179, 92JPR483; 94H1299; 96KFZ36]. In this way all the other isomeric thienopyridines (**245–247**) also were accessible (87JHC85) (Scheme 62). This method also allowed two thiophene rings (**248**) (94H1299) to be constructed when two *o*-chloronitrile units were present in the starting material (Scheme 62). Moreover, a 3-amino-2-phenylthieno[2,3-*c*]pyridine analogous to **246** was readily formed with benzylmercaptan in the presence of NaOEt in spite of the weak CH acidity of the benzylthio group (83T4153). Thienopyridines **244** and **246** could also be prepared from the corresponding bromocyanopyridines and ethyl thioglycolate under irradiation and in the presence of *t*-BuOK (83T4153).

Thorpe-Ziegler cyclization was further applied to the 1,4-dihydropyridine series (87KGS124; 88ZOR460; 92KFZ40; 93DOK1597; 96KGS553) (see **249**, **250**). Unless the 4-position is disubstituted as in the case of dihydropyridothio-*phene* (**253**) (96IZV2535), there is the possibility that fully conjugated

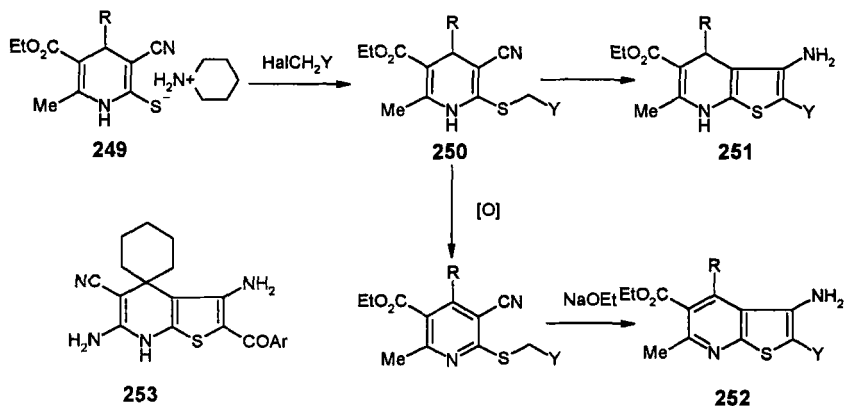




SCHEME 62

thieno[2,3-*b*]pyridines (**252**) (87KGS124) are formed rather than the expected dihydro derivatives (**251**), due to the easy oxidation of **251** (Scheme 63).

By routes similar to those for thienopyridines, thieno[2,3-*d*]pyrimidines (**257**), thieno[2,3-*c*]pyridazines (**261**) (via **260**), and thienoquinoxalines (**265**) (via **264**) were synthesized via Thorpe–Ziegler cyclizations, starting materials include the *o*-cyanothiones **254** (via **256**) [84JCS(P1)2447; 91PS(60)223; 92KGS1280; 96T1011], **258** [90JPR104, 90MI3; 91M413, 91ZN(B)835; 94PS203], and **262** [91PS(61)151; 93PS(79)77], which are alkylated, or the *o*-chloronitriles



SCHEME 63

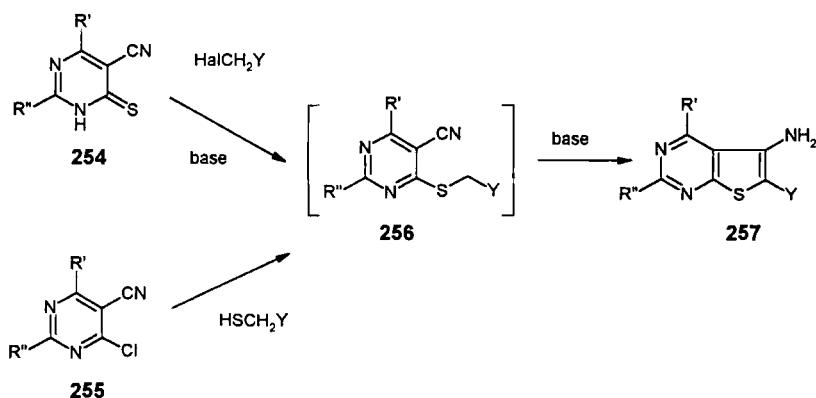
**255** (87KGS1131; 88JHC959, 88KGS1559, 88LA633; 90JHC717), **259** [90JPR104, 90MI3; 91M413; 91ZN(B)835; 94PS203], and **263** [91PS(61)151; 93PS(79)77], which are substituted (Schemes 64–66). The thieno[2,3-*b*]pyrazine **266** (89JA285) could be obtained in a similar manner from the corresponding *o*-chloronitrile precursor (Scheme 67).

The formation of thieno[2,3-*d*]pyrimidine **269** (Scheme 68) does not follow general path of Scheme 64 because the Thorpe–Ziegler precursor **268** was generated by ring opening of the starting aminoisothiazole (**267**) in the presence of chloroacetone as alkylating reagent [88JCR(S)46].

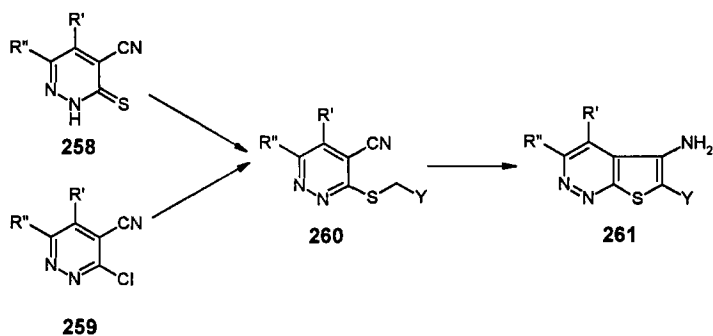
## V. Synthesis of 3-Aminoselenophenes

2-Aminoselenophenes (**273**) were synthesized starting from  $\beta$ -chlorocinnamionitrile (**270**) by selenylation/alkylation and then Thorpe–Ziegler cyclization (92M455) of **272** (Scheme 69). The unstable 3-selenylcinnamionitrile **271** was not isolated.

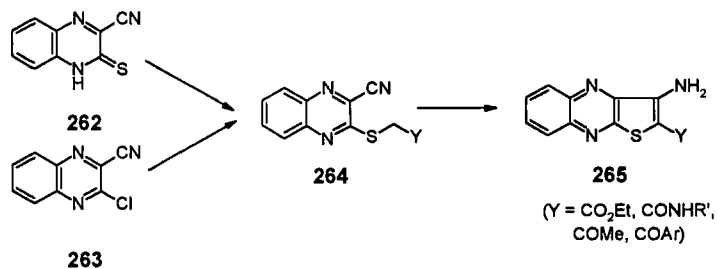
Pyridine-2-selenones (**274**) are more stable and served as precursors (via **275**) for selenopheno[2,3-*b*]pyridines (**276**) (84IZV2760, 84KGS708, 85S98, 85ZOB1656; 86IZV406; 88KPS138; 89CS327, 89ZOB881; 90ZOB2384, 90ZOB2750; 91ZOB747, 91ZOB942; 93PS(82)691; 94KGS122) (Scheme 70). The substituted methylselenopyridines are more prone to Thorpe–Ziegler cyclization than the corresponding methylthiopyridines (**220**) (94KGS122) (Scheme 56). The dihydroselenopheno[2,3-*b*]pyridine **277** was obtained in the same way (91ZOB948) (Scheme 70).



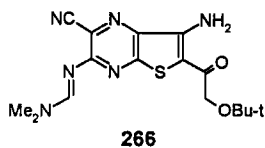
SCHEME 64



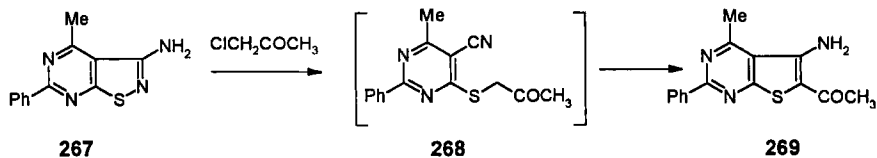
SCHEME 65



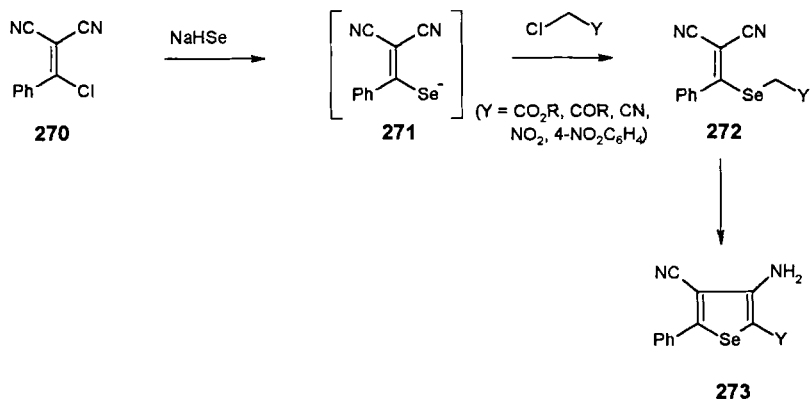
SCHEME 66



SCHEME 67



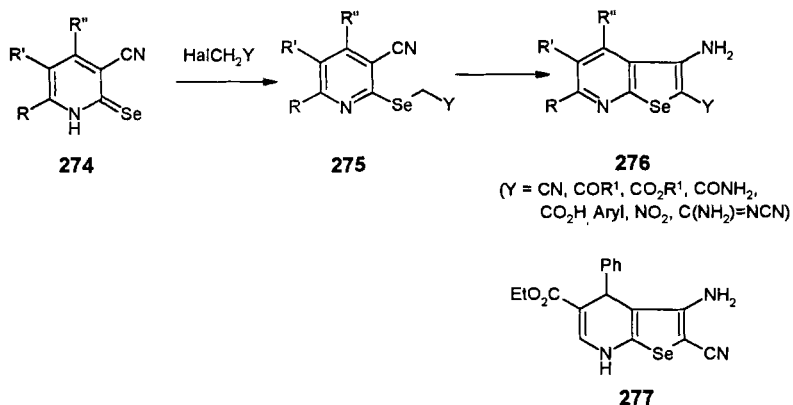
SCHEME 68



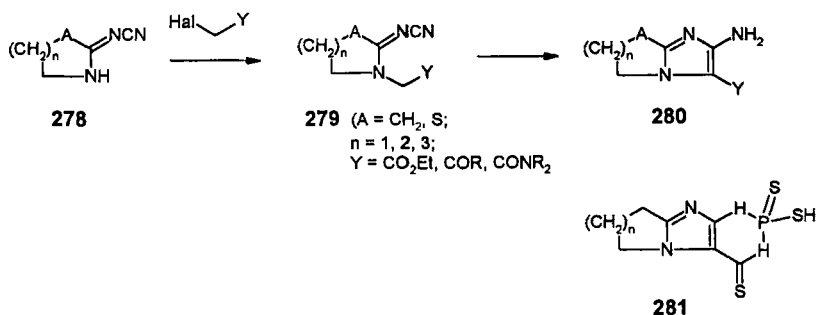
SCHEME 69

## VI. Synthesis of Aminoazoles

Thorpe–Ziegler cyclization can also be applied to the synthesis of azoles (**1**) with X or Y as N atoms (see Scheme 1). The majority of known examples started with cyanamide derivatives **1** ( $\text{X} = \text{N}$ ) and hence provided 1,3-azoles. Thus, semicyclic cyanamidine structures **278** could be alkylated at the ring N atom in the presence of a base (e. g.,  $\text{NaH}$ ), giving the Thorpe–Ziegler precursors **279** that led to the condensed aminoimidazoles **280** [ $\text{A} = \text{CH}$  (91LA975, 91KGS754),  $\text{A} = \text{S}$  [85JAP(K)60/28982, 85JAP(K)60/51194, 85JAP(K)60/51195; 88S261; 92KFZ62]] (Scheme 71). Imidazo-1,3,2-diaza-



SCHEME 70



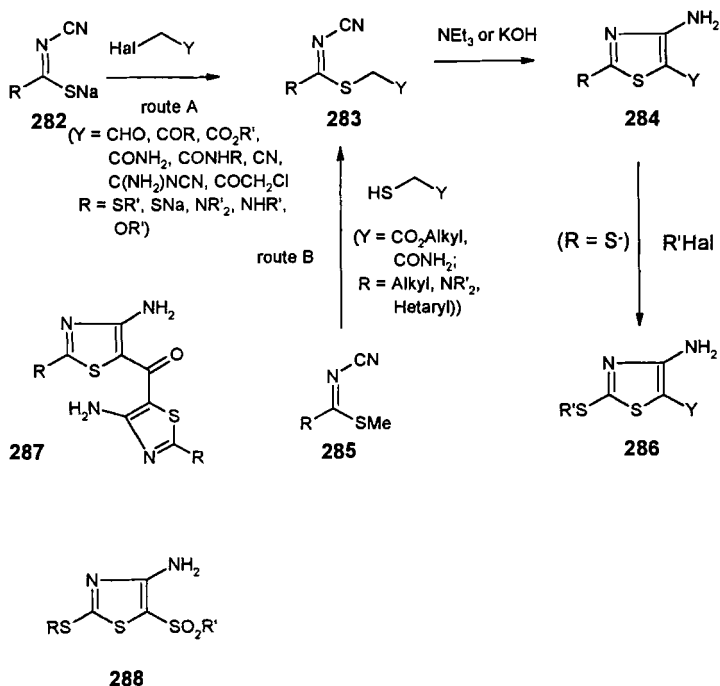
SCHEME 71

phosphorines (**281**) were obtained when intermediate amides (**279**; A = CH<sub>2</sub>, Y = CONH<sub>2</sub>) were treated with P<sub>4</sub>S<sub>10</sub> in pyridine (92KFZ63, 95MC67).

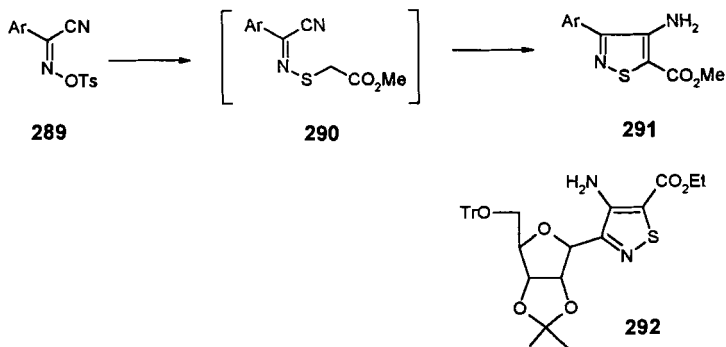
*N*-Cyanoisothioamide, precursors for the synthesis of 4-amino-1,3-thiazoles, are available by various routes. For example, *N*-cyanoisothioamides (**282**) were alkylated, giving **283** (route A) and, after cyclization, thiazoles (**284**) (83BCJ3851, 83JOC3340, 83ZC179; 84H697, 84JHC1361; 86JHC1435; 89EUP301613; 90MIP1; 91SL179; 95ZOR127; 96T1011) (Scheme 72). In the same manner bisaminothiazolyketones (**287**) could be obtained by a twofold Thorpe–Ziegler reaction using one equivalent of 1,3-dichloroacetone as the alkylating reagent (Y = COCH<sub>2</sub>Cl) and two equivalents of **282** (86JHC1435). Sometimes no extra base was necessary for the synthesis of the thiazoles **284** according to route A. If cyanimidodithiocarbonates (**282**; R = SNa) were used, Thorpe–Ziegler cyclization to **284** was followed by *S*-alkylation, affording thiazoles **286** (84CCC2285). Sulfones (**288**) were obtained from the corresponding *S*-chloromethyl-*N*-cyanoisothioamides (**283**; Y = Cl) by nucleophilic substitution with R'SO<sub>2</sub>Na and Thorpe–Ziegler cyclization (89EGP253424).

Alternatively, 4-amino-1,3-thiazoles (**284**) could be synthesized according to route B, on substitution of the methylthio group in *S*-methylisothioamides **285** by  $\alpha$ -mercaptocarbonyl compounds (86LA780; 87S940; 95G115) (Scheme 72). Thorpe–Ziegler cyclization of thiooximes (**290**) of acylcyanides gave access to 4-aminoisothiazoles such as **291** (82EUP48615) (Scheme 73). The former were obtained from the corresponding *O*-tosyloximes (**289**) and mercaptoacetate. In the same manner the *C*-glycoside **292** was obtained (93JOC5181).

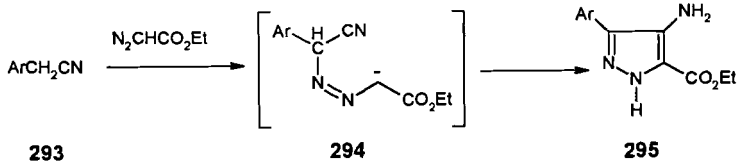
The interaction of ethyl diazoacetate with benzylcyanides (**293**) opened a straightforward way to aminopyrazoles (**295**) (84FES618), probably via azo intermediates **294** (Scheme 74).



SCHEME 72



SCHEME 73



SCHEME 74

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# 1,2,4-Triazolo- and Tetrazolo[x,y-z]pyrimidines

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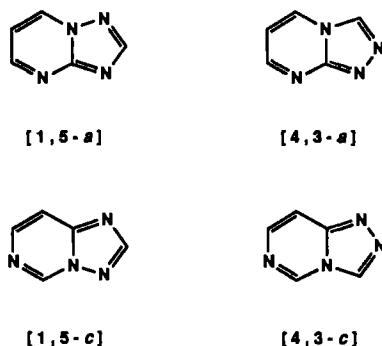
I. Introduction . . . . .	127
II. 1,2,4-Triazolo[x,y-z]pyrimidines . . . . .	127
A. 1,2,4-Triazolo[1,5-a]pyrimidines . . . . .	128
B. 1,2,4-Triazolo[4,3-a]pyrimidines . . . . .	171
C. 1,2,4-Triazolo[1,5-c]pyrimidines . . . . .	184
D. 1,2,4-Triazolo[4,3-c]pyrimidines . . . . .	197
III. Tetrazolo[x,y-z]pyrimidines . . . . .	202
A. Tetrazolo[1,5-a]pyrimidines . . . . .	202
B. Tetrazolo[1,5-c]pyrimidines . . . . .	208
References . . . . .	211

## I. Introduction

This chapter reviews the chemistry, biological significance, and uses of 1,2,4-triazolo- and tetrazolo[x,y-z]pyrimidines. The arrangement of each ring follows the order of the site of fusion on the pyrimidine ring, denoted by the letter z, and the site of fusion on the triazole ring, denoted by the letters x and y. The classification of the subdivisions is dependent upon the extent of published work. Reviews on 1,2,4-triazolo[1,5-a]pyrimidines (90ZC305; 93AHC81), azaindolizines (77HC188), and systems with [3,4-z] ring junction (90AHC277) were published. Azido-tetrazolo isomerization was reviewed (69CRV345; 73S123). The subject was also covered in "Comprehensive Heterocyclic Chemistry" [84CHEC(1)847]. The present chapter reviews the work on the title compounds from 1980 to the end of 1995 (*Chemical Abstract* volume **123**) with some additional earlier references.

## II. 1,2,4-Triazolo[x,y-z]pyrimidines

Four isomeric structures are possible. All of them have a bridgehead nitrogen atom. A characteristic feature in these triazolopyrimidines is the ease of a Dimroth rearrangement (99AHC) in two systems; this results in the



SCHEME 1

conversion of 1,2,4-triazolo[4,3-*a*]- and [4,3-*c*]pyrimidines to the isomeric 1,2,4-triazolo[1,5-*a*]- and [1,5-*c*]pyrimidines, respectively (Scheme 1).

### A. 1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

Synthesis of this ring may be achieved by the construction of one of the heterocycles followed by using it as a basis to build the other ring onto it or by the Dimroth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines. 1,2-Diaminopyrimidines are general precursors, and they can be generated from 1-amino or 2-aminopyrimidines. The 3- and 5-amino-1,2,4-triazoles are alternative precursors that can act as a source of three carbons to complete the pyrimidine ring.

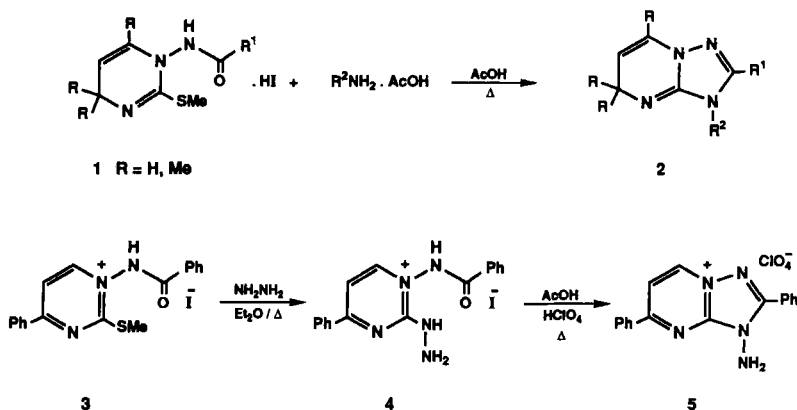
#### 1. *Synthesis from 1-Aminopyrimidines*

Cyclization of 1-(acylamino)pyrimidine hydroiodides (**1**) with alkyl ammonium acetates gave 3*H*,5*H*-1,2,4-triazolo[1,5-*a*]pyrimidines (**2**) (87 EGP246999; 89ZC378). Condensation of the 1-(acylamino)pyrimidinium salt **3** with hydrazine hydrate gave **4**, which upon cyclization with acetic acid in the presence of perchloric acid afforded the 3-amino-1,2,4-triazolo[1,5-*a*]pyrimidinium salt **5** (89EGP270711) (Scheme 2).

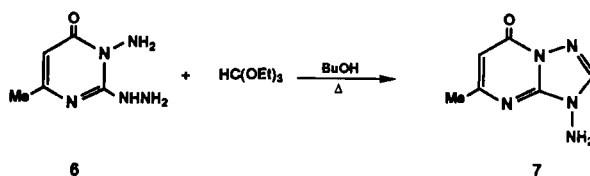
The 1-amino-2-hydrazinopyrimidine **6** can be cyclized with triethyl orthoformate to **7** (85USP4546181) (Scheme 3).

#### 2. *Synthesis from 2-Aminopyrimidines*

Amination of 2-aminopyrimidine (**8**) with *O*-mesitylenesulfonylhydroxylamine (NH<sub>2</sub>OMes) gave the *N*-aminopyrimidinium salt **9**, which can be



SCHEME 2



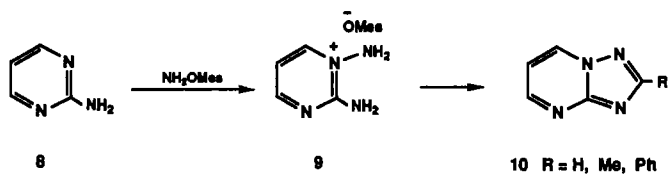
SCHEME 3

transformed into 1,2,4-triazolo[1,5-*a*]pyrimidines (**10**) by heating with formic acid, acetic anhydride, and benzoyl chloride (75JHC107) (Scheme 4).

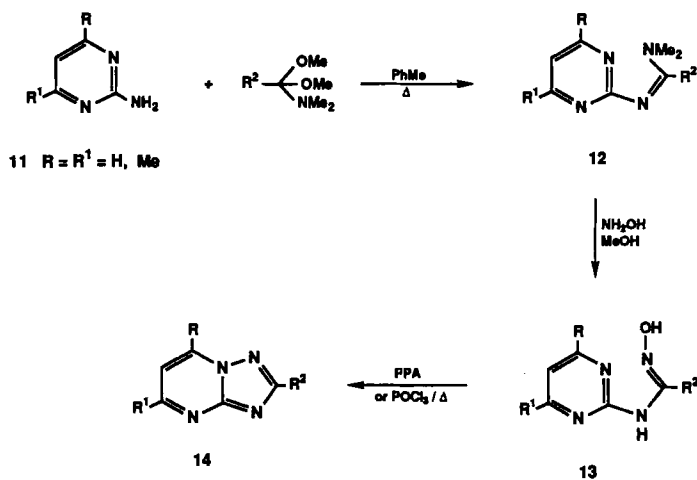
The synthesis of triazolopyrimidines may be achieved by the cyclization of 2-aminopyrimidines by fusion of a C–N fragment. Thus, the triazolopyrimidines (**14**) have been prepared by the sequential condensation of 2-aminopyrimidines (**11**) with  $(MeO)_2CR^2NMe_2$  followed by reaction of the resulting derivative **12** with  $NH_2OH$  to give the hydroxyiminomethyleneaminopyrimidine **13**, which was cyclized by the action of polyphosphoric acid (PPA) [74JOC2143; 81JAP(K)81/127383; 82JHC577]. In the case of 2-amino-4-methylpyrimidine as a starting compound, cyclization involved either an N-1 or N-3 atom of the pyrimidine, whereby both isomers were formed in a ratio of 1:5; the major one has  $R^1 = Me$  (73TL1677) (Scheme 5).

2-Aryl-1,2,4-triazolo[1,5-*a*]pyrimidines (**17**) were prepared by oxidative cyclization, by the action of lead tetraacetate (LTA), of 2-pyrimidylarylamidines (**16**), first prepared by the reaction of 2-aminopyrimidines (**15**) with aryl cyanides in the presence of  $AlCl_3$  (90SC2617) (Scheme 6).

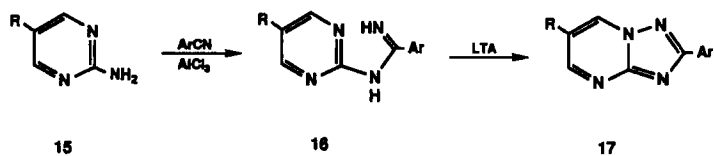
Treatment of 2-(aroylamino)pyrimidines (**18**), prepared from **15** and aroyl chlorides with  $PCl_5$  followed by azidolysis in aqueous acetone, gave the tetrazoles **19**, whose subsequent pyrolysis afforded 2-aryl-1,2,4-



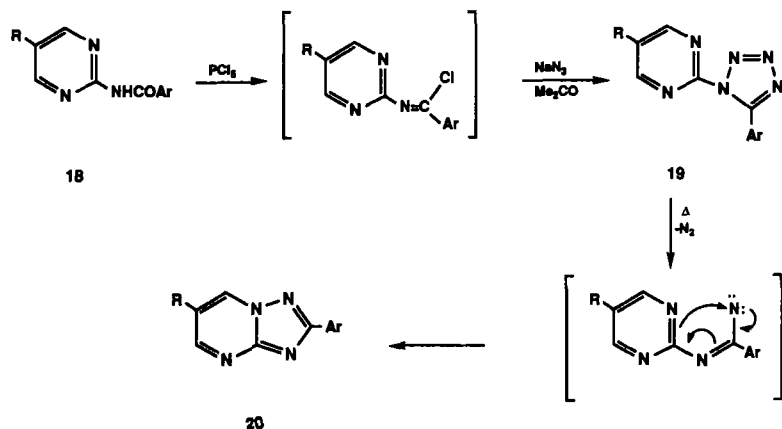
SCHEME 4



SCHEME 5



SCHEME 6



SCHEME 7

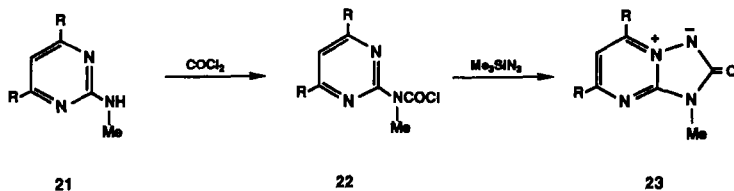
triazolo[1,5-*a*]pyrimidines (**20**). A pathway for the formation of **20** from **19** involved the elimination of a molecule of nitrogen from **19** followed by cyclization of the resulting nitrene intermediate (88BCJ3791) (Scheme 7).

The 1,2,4-triazolo[1,5-*a*]pyrimidinium-2-olates (**23**) were prepared by the sequential reaction of 2-methylaminopyrimidines (**21**) with phosgene to give **22** followed by  $\text{Me}_3\text{SiN}_3$  [87JCS(CC)112] (Scheme 8).

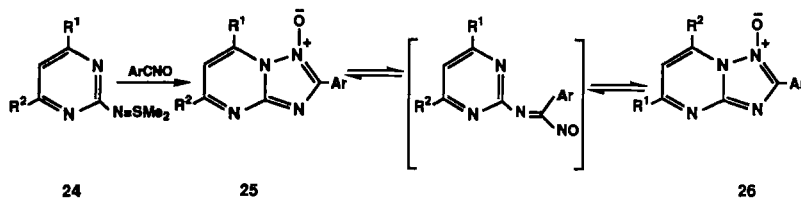
Reaction of pyrimidinolsulphimides (**24**) with nitrile oxide at room temperature gave the triazolopyrimidine *N*-oxides (**25**), which underwent a reversible, degenerate valence tautomerism at 90–110°C involving the nitrosoimine tautomer as an intermediate to give the isomer **26** [74JCS(CC)486; 76JCS(P1)2166] (Scheme 9).

### 3. Synthesis from 5(3)-Amino-1,2,4-Triazoles

5-Amino-1*H*-1,2,4-triazole and its derivatives are frequently used as precursors for this ring via their reaction with suitable carbonyl compounds. The 5-amino-1,2,4-triazoles (**27**), prepared from calcium cyanide by hydrolysis to cyanamide followed by condensation with hydrazine (92MI4), reacted with the appropriate acetophenone in presence of  $\text{ZnCl}_2$  to give the



SCHEME 8

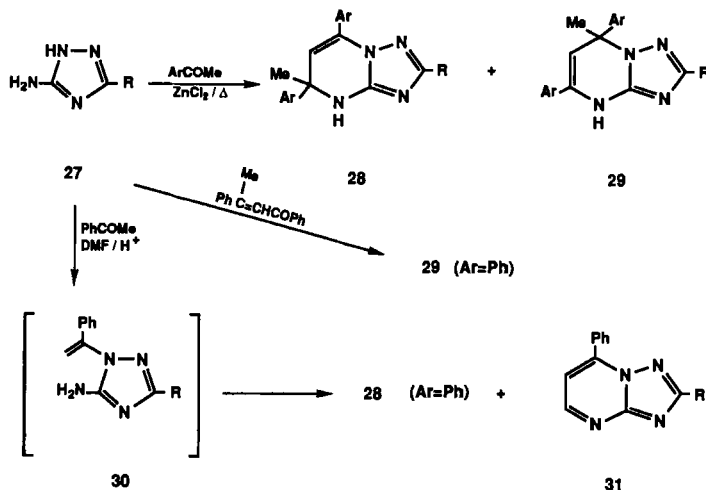


SCHEME 9

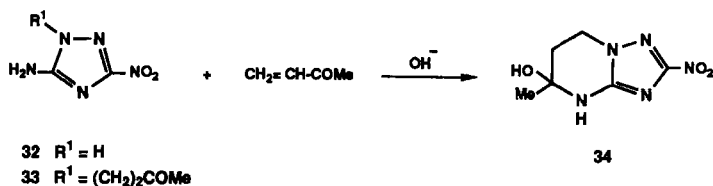
dihydrotriazolopyrimidines **28** and **29** [86JAP(K)61/227584; 91S189]. Cyclocondensation of **27** with acetophenone in DMF gave the triazolopyrimidines **28** (Ar = Ph) and **31** via the intermediate **30** by participation of either a second acetophenone molecule or a DMF molecule, respectively. The reaction of **27** with PhCMe=CHCOPh in the absence of a catalyst afforded the dihydrotriazolopyrimidines **29** (Ar = Ph) (92DOK801) (Scheme 10).

The reaction of 5-amino-1,2,4-triazole with  $\beta$ -dimethylaminopropiophenone, aromatic aldehydes and acetophenones, or substituted vinyl aryl ketones gave the 5,7-disubstituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidines (89KGS1000; 91KGS1539; 93KGS481, 93KGS1353, 93KGS1357, 93KGS1433). The cyclization of **32** with methyl vinyl ketone in the presence of a base gave the tetrahydrotriazolopyrimidine **34**, which was alternatively formed, from **33** by the action of alkali (94ZOR774) (Scheme 11).

Cyclization of **27** with 1,3-dicarbonyl compounds gave **37** (60JCS1829; 82JMC420; 83JHC735; 86EUP150974, 86EUP188225; 89USP4822404;



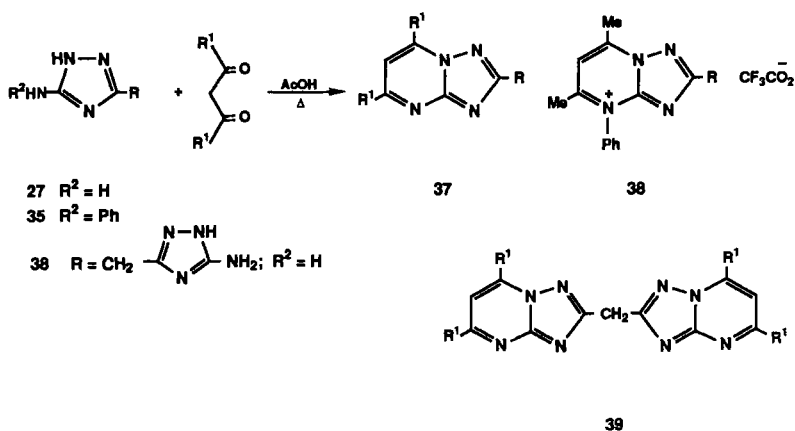
SCHEME 10



SCHEME 11

93JHC169). Similarly, the bis(aminotriazolyl)methane **36** gave the bis(triazolopyrimidyl)methane **39** (82UKZ79). Reaction of the 5-anilino derivative **35** with acetylacetone in the presence of TFA gave the triazolopyrimidinium salt **38** (88UKZ880). The use of unsymmetrically substituted acetylacetone having a bulky electron-withdrawing group led to a mixture of triazolo[1,5-*a*]pyrimidine isomers. Steric factors have a dominant influence in the regiochemical outcome. The ratio of products is influenced much more by the inductive effect of the substituent **R** in **27**. In the reaction with triacetyl methane and 3-(4-chlorobenzoyl)acetylacetone, the elimination of a 1-acetyl group from the reactant gave the 6-acetyl triazolopyrimidine together with the deacetylated derivative. A mixture of 5-methyl and 7-methyl-6-acetyl-1,2,4-triazolopyrimidine isomers was formed from the reaction of ethoxymethyleneacetylacetone with **27**. A linear hept-2,4,6-trione behaved as a simple 1,3-diketone on reaction with **27** (95JHC407) (Scheme 12).

The triazolopyrimidine-2-sulfonamides **45** were prepared from the 1,2,4-triazole **40** by reaction with phenyl chloroformate to give **41**, whose chlorination gave **42**, then transformed to the amide **43**. Hydrolysis of

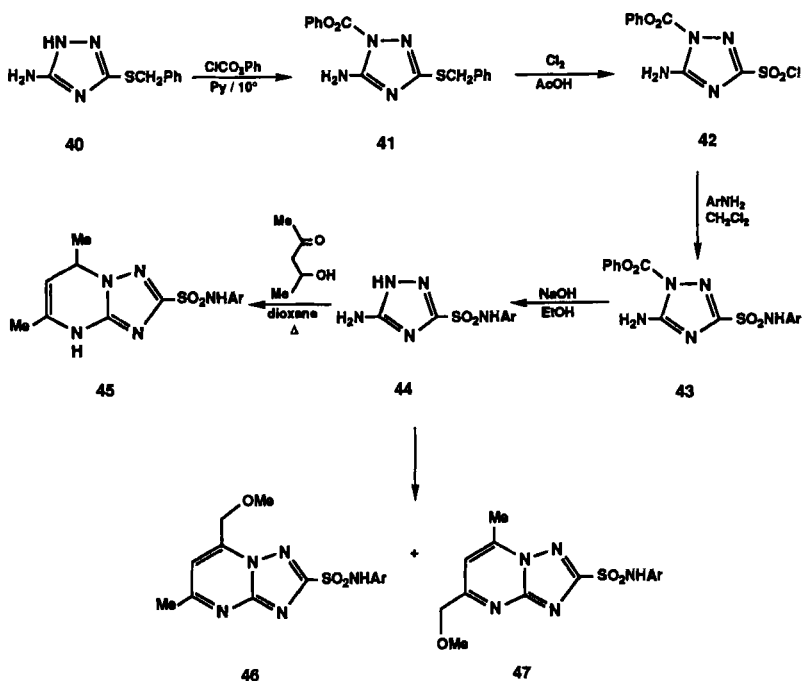


SCHEME 12



the latter compound gave the 1*H*-triazole sulfonamide **44**, whose cyclization with 4-hydroxy-2-pentanone in dioxane gave **45** (89EUP332029; 93JHC169). Heating **44** with unsymmetrical 1,3-dicarbonyl compounds such as 1-methoxyacetylacetone in the presence of acetic acid provided a mixture of **46** and **47** (88GEP3640155). A similar reaction in presence of piperidine at 0–5°C afforded only **46** (90GEP3843849) (Scheme 13).

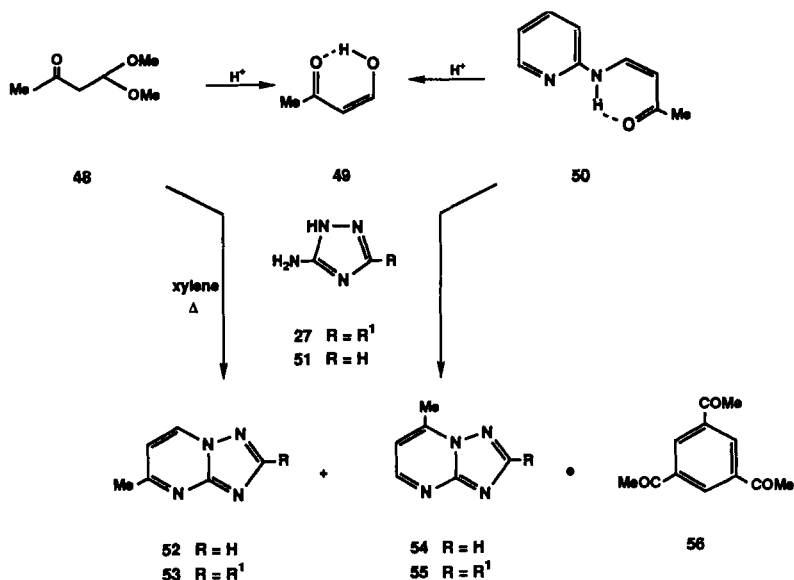
Reaction of 4,4-dimethoxybutan-2-one (**48**) with 5-amino-1,2,4-triazole (**51**) in boiling xylene has been reported to furnish 5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**52**) (59JOC796), but this condensation in boiling acetic acid or in toluene in the presence of *p*-toluenesulfonic acid [79JCS(P1)3085] gave 5-methyltriazolopyrimidine (**52**) accompanied by the isomer, 7-methyltriazolopyrimidine (**54**) and the self-condensation product 1,3,5-triacetylbenzene (**56**). Similarly, **48** and **27** gave **53**, **55**, and **56**. A regioselective synthesis of the 5-methyl isomer took place exclusively in the presence of sodium ethoxide (89JHC1393) or in aqueous base (91USP4988812). The proposed mechanism indicated that the  $\beta$ -ketoacetal **48** was initially converted to 3-oxobutanal (**49**) by hydrolysis under the acidic conditions. Thus, there are two possible sites for the condensation of



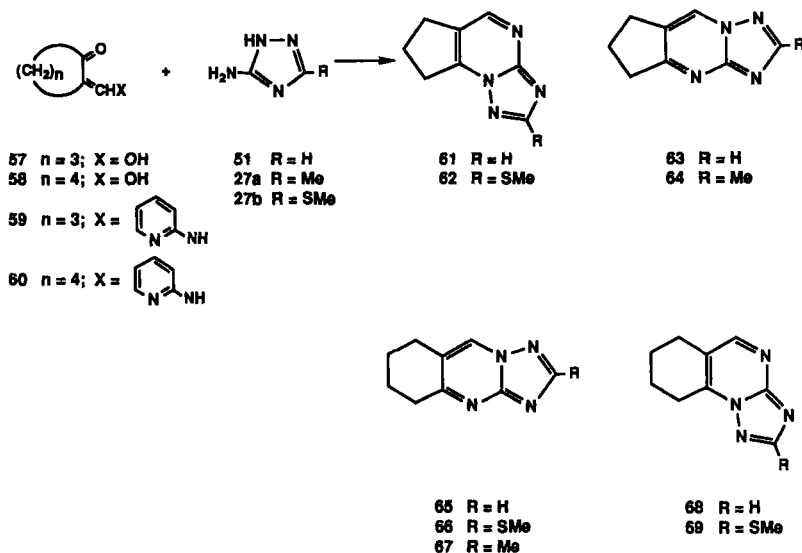
SCHEME 13

the aminotriazole with **49**; the amino group of the triazole can react with the aldehyde carbonyl group to give the 7-methyl isomers or with the keto group to give the 5-methyl isomers (89JHC1393). The reaction of the ketoanil 2-(2-acetylvinylamino)pyridine (**50**) with **51** was catalyzed by *p*-toluenesulfonic acid to give a 20% yield of **52**; the amino group of **51** condensed with the carbonyl group of **50** prior to cyclization and displacement of the 2-aminopyridine. Some of the product from this condensation (**54**) was formed when the ketoanil **50** underwent a preliminary *retro*-anil reaction to yield 3-oxobutanal (**49**) prior to the condensation with **51**. The ratio of **52** to **54** was dependent on the catalyst identity. With anhydrous oxalic acid the preliminary *retro*-anil reaction was suppressed, and **52** became the predominant product (70%) (Scheme 14).

The carbocyclic analogs were prepared by the reaction of 5-aminotriazole (**51**) and 5-amino-3-methylthio-1,2,4-triazole (**27b**) with 2-hydroxymethylenecyclopentanone (**57**) to furnish the angularly fused cyclopenta[*e*]triazolopyrimidines **61** and **62**, respectively. However, reaction of 2-hydroxymethylenecyclohexanone (**58**) with the aminoazoles **51** and **27b** afforded both the linear and the angular cyclohexatriazolopyrimidines **65** and **66** and **68** and **69**, respectively. Reaction of 5-amino-3-methyl-1,2,4-triazole (**27a**) with **58** gave only the linear product **67** [50RTC343; 79JCS(P1)3085]. Condensation of 2-(2-pyridylaminomethylene)cyclopenten-



SCHEME 14



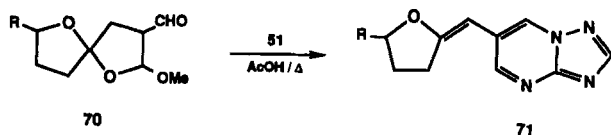
SCHEME 15

tanone (**59**) with **51** and **27a** gave the linearly fused condensation products **63** and **64**, respectively. The condensation of **60** with **27b** afforded a mixture of a linearly fused product (major) and an angularly fused one (minor). However, when the catalyst *p*-toluenesulfonic acid was replaced by anhydrous oxalic acid in the condensation of **60** with **27b**, a high yield of the linearly fused compound **66** was obtained [79JCS(P1)3085] (Scheme 15).

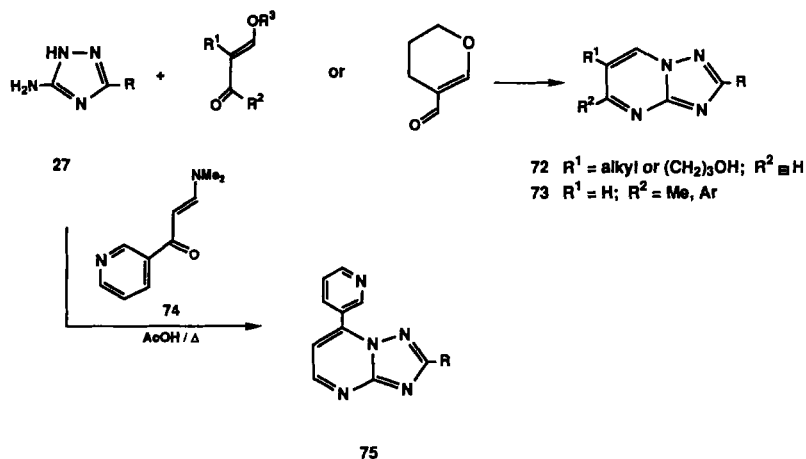
Reaction of 3-formyl-2-methoxy-1,6-dioxaspiro[4.4]nonanes (**70**) with **51** gave **71** (93IZV2004) (Scheme 16).

Cyclization of 3-alkoxyacrolein, 5,6-dihydro-4*H*-pyran-3-carboxaldehyde, or unsaturated ketones with **27** in the presence of a base afforded the triazolo[1,5-*a*]pyrimidine derivatives **72** or **73** (80USP4209621; 83S44; 91USP4988812). Reaction of **74** with **27** in the presence of AcOH gave **75** (84USP4444774; 86USP4582833) (Scheme 17).

Reaction of **51** with the unsaturated ketone **76** was dependent upon the reaction conditions (90MI1). Thus, **77** and **78** were formed in different ra-



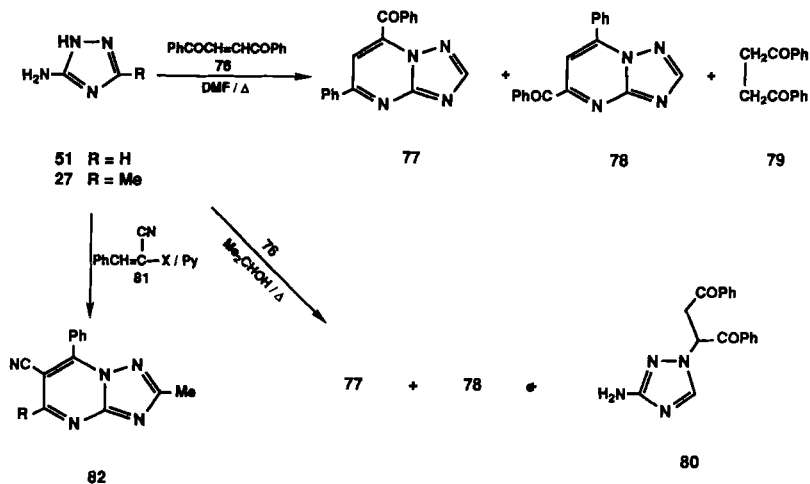
SCHEME 16



SCHEME 17

tios, with by-products **79** and **80** formed depending upon the solvent. The condensation of **27** with the unsaturated ketone or nitrile **81** ( $X = C(=O)Ph$  or  $CN$ ) gave **82** ( $R = Ph$  or  $NH_2$ ) [88IJC(B)421] (Scheme 18).

When ethyl  $\beta$ -ethoxy- $\alpha$ -ethoxycarbonylacrylate **84** ( $R^2 = H$ ) was condensed with the *N*-substituted aminotriazole **83** in boiling acetic acid, it gave the triazolopyrimidin-7-ones **85** ( $R^2 = H$ ) and the by-product **87**, but the condensation of **84** ( $R^2 = Me$ ) with **83** gave a mixture of the triazolopyrimidin-7-one **85** ( $R^2 = Me$ ) and the isomeric triazolopyrimidin-5-

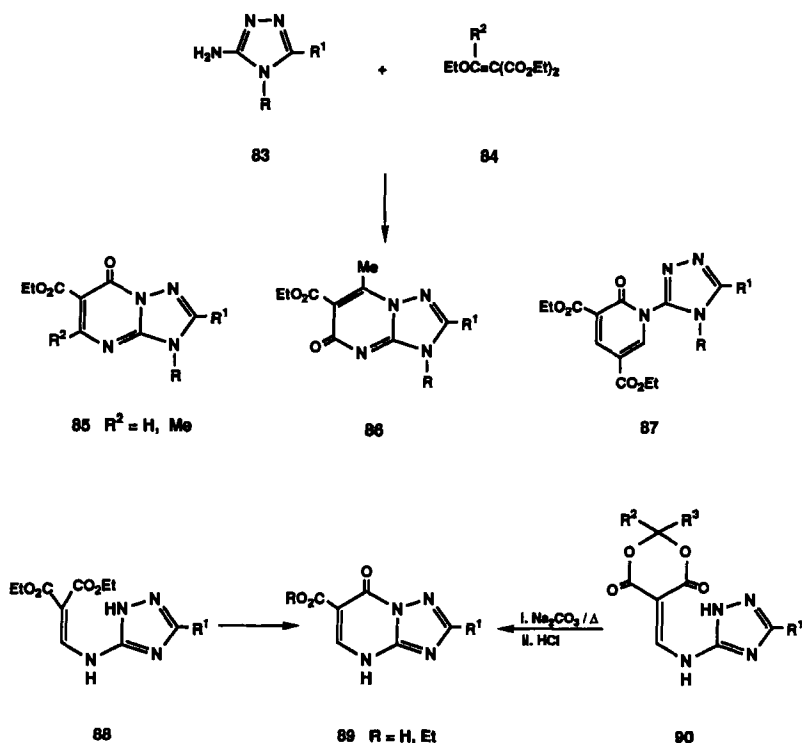


SCHEME 18

one **86** [67JCS(C)503]. When the reaction of **83** ( $R = H$ ) with **84** was carried out in boiling acetic acid, the enolized form of **85** was obtained [80JCS(P1)1347; 82JMC420].

The 7-oxotriazolopyrimidine **89** was prepared by cyclizing triazolyaminomethylenemalonate (**88**) by the action of polyphosphoric ester (93MI2) or by treatment of [(triazolylamino)methylene]dioxanediones (**90**) with  $Na_2CO_3$  followed by saponification with  $HCl$  (91USP5061799) (Scheme 19).

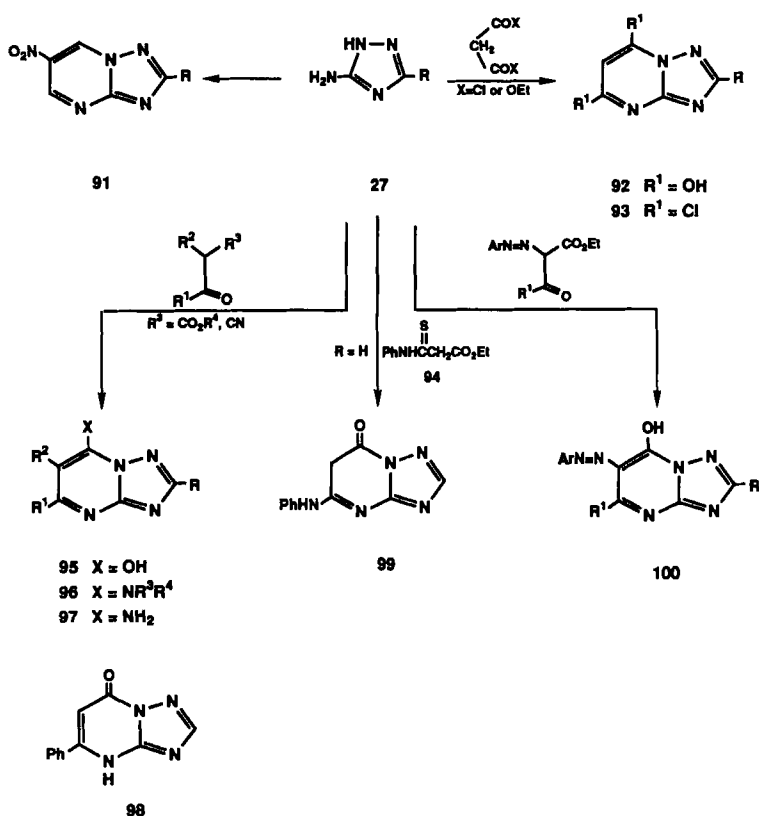
Cyclocondensation of the sodium salt of nitromalondialdehyde (86 KFZ947), malonyl chloride or diethyl malonate (91USP5006656), malonic acid in phosphorus oxychloride (89EUP332029; 93JHC169), and  $\beta$ -ketoesters in  $AcOH$  (82MIP1; 90EGP276620) with **27** gave the nitro derivative **91**, the 5,7-dihydroxy derivative **92**, the chloro derivative **93**, and the hydroxy derivative **95**, respectively. Ring closure of **51** with ethyl benzoyleacetate in the presence of  $NaOEt$  gave the triazolopyrimidine **98**, a tautomer of **95** (85JHC601). Chlorination of **95** followed by amination gave the



SCHEME 19

amine **96** [80JAP(K)80/51089; 82JAP82/35592; 83MIP1; 85GEP3338292, 85MIP1; 86EUP190375; 87GEP3534650, 87GEP3534651, 87T2497; 88 IJC(B)825]. Alternatively, condensation of **27** with  $\beta$ -ketonitrile gave the amine **97** (87GEP3533050). Reaction of **27** with  $\alpha$ -aryldazo derivatives of  $\beta$ -ketoesters gave **100** (85H2251; 91CCC1560). A similar reaction using ethyl acetoacetate *p*-sulfonylphenylhydrazones with **51** provided the tautomer of **100**, namely-5-methyl-6-(*p*-sulfonylphenylazo)-1,2,4-triazolo[1,5-*a*]pyrimidin-7(4*H*)-one (95PHA33). The interaction of the phenylthiocarbamyl derivative **94** with 5-amino-1,2,4-triazole resulted in the formation of triazolo[1,5-*a*]pyrimidine (**99**) (92JSC165) (Scheme 20).

Condensation of the 4-allylaminotriazole **101** with ethyl acetoacetate by heating without a solvent gave the triazolopyrimidines **103a** and **104a** in compatible yields, whereas when glacial acetic acid was employed as a solvent only **103a** was obtained. Heating the 5-allylaminotriazole **105** with

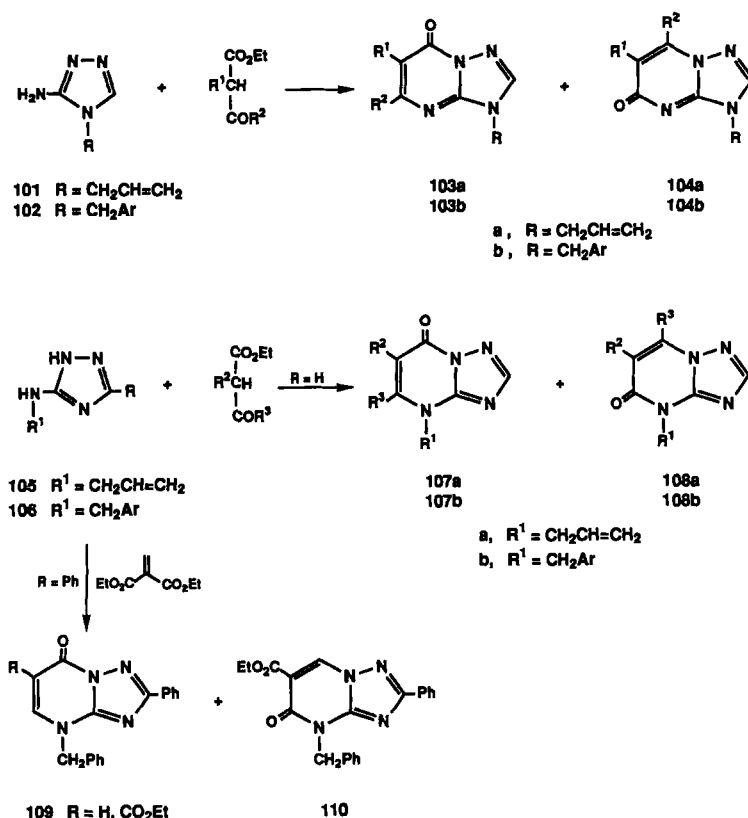


SCHEME 20

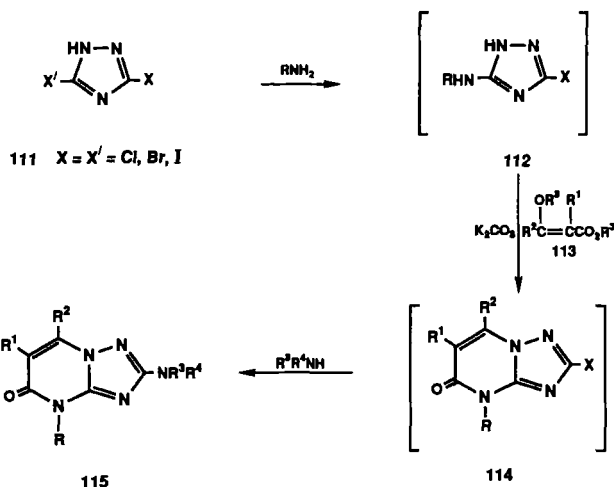
ethyl acetoacetate without a solvent or in glacial acetic acid afforded the triazolopyrimidines **107a** and **108a** (63CPB851). Similarly, reaction of the *N*-benzyl derivative **102** with  $\beta$ -ketoesters gave **103b** and **104b**, whereas **106** gave **108b** in the absence of acetic acid and **107b** in acetic acid (68T2839). Condensation of ethyl  $\alpha$ -ethoxycarbonylacrylate with 5-benzylamino-3-phenyl-1,2,4-triazole (**106**, Ar = Ph) in boiling acetic acid afforded a mixture of 4-benzyl-6-ethoxycarbonyl-2-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**109**, R = CO<sub>2</sub>Et), its decarbethoxy derivative (**109**, R = H), and its 5-one-isomer **110** (68T2839) (Scheme 21).

2-Amino-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives (**115**) were prepared from 3,5-dihalo-1,2,4-triazoles (**111**) by amination followed by reaction with acrylic or crotonic ester (**113**) and then amination without the isolation of **112** and **114** [87T2497; 88JAP(K)63/267782] (Scheme 22).

Reaction of **27** with ethyl  $\alpha,\beta$ -dibromopropionate in boiling pyridine led to the triazolylacrylate **116**, which was cyclized with NaOEt to 5-hydroxy-



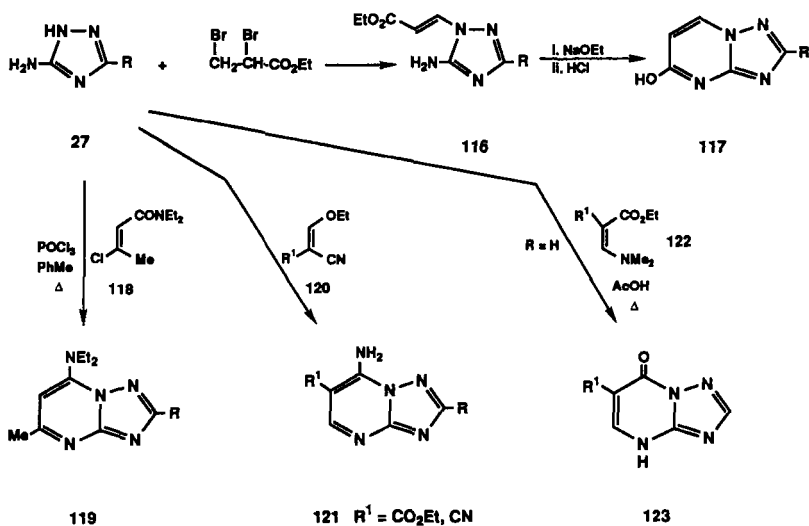
SCHEME 21



SCHEME 22

triazolopyrimidine **117** [67JCS(C)503]. Cyclocondensation of **27** with the unsaturated amide **118** gave **119** (81JAP81/108772), and with ethyl 2-cyano-3-ethoxyacrylate or 2-cyano-3-ethoxyacrylonitrile (**120**) gave **121** (87JHC1149). Heating **51** with the acrylate derivative **122** in acetic acid formed the dihydrotriazolopyrimidine **123** (91CPB1099) (Scheme 23).

Condensation of **27** with 2-amino-3-ethoxycarbonyl-4,5-dihydrofuran



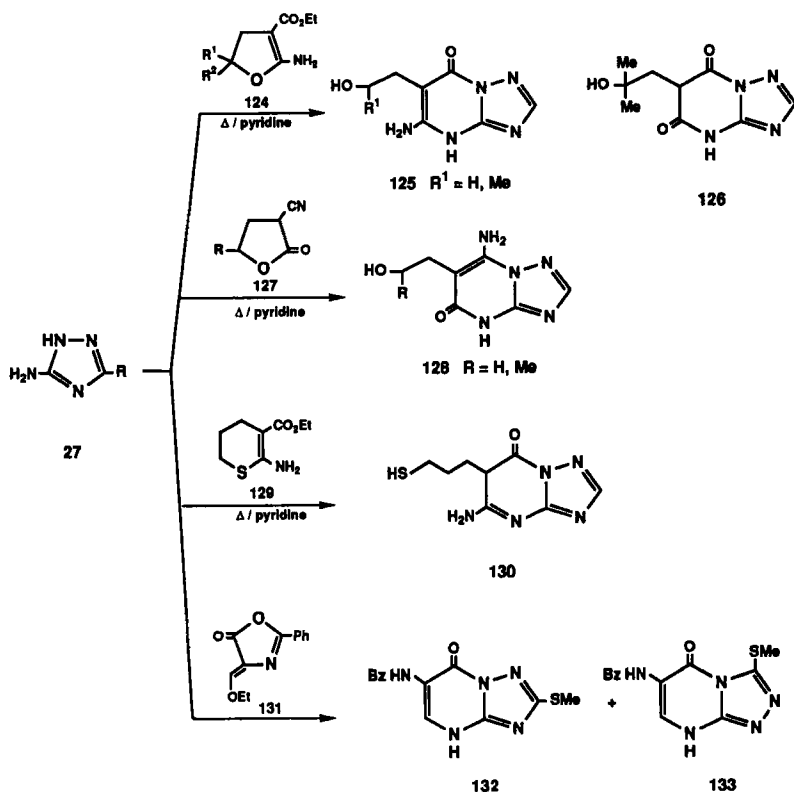
SCHEME 23



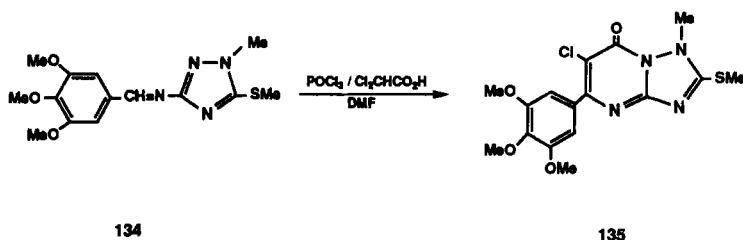
(**124**,  $R^1 = R^2 = H$ ) gave the triazolo[1,5-*a*]pyrimidines (**125**), but with **124** ( $R^1 = R^2 = Me$ ) afforded the dioxo derivative **126**, and with  $\alpha$ -cyano- $\gamma$ -butyrolactones (**127**) or 2-amino-3-ethoxycarbonyl-5,6-dihydro-4*H*-thiopyran (**129**) gave the triazolopyrimidines **128** and **130**, respectively (81JHC1287). Treatment of 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (**131**) with 5-amino-3-methylthio-1*H*-1,2,4-triazoles gave the triazolo[1,5-*a*]pyrimidinone **132** and the [4,3-*a*] isomer **133** (93H955) (Scheme 24).

The Schiff base **134** with the mixture of phosphorus oxychloride and dichloroacetic acid in DMF led to the triazolopyrimidinone **135** instead of the expected 3,3-dichloroazetidinone derivative (88JHC173) (Scheme 25).

Unsymmetrical vinamidinium salt **137** can be cyclized with **51** at low temperature to give the 7-substituted isomer **138**, but at higher temperature isomers **138** and **139** were both obtained. When the chloropropeniminium salt **136** was used under similar conditions, compound **138** was formed. The



SCHEME 24



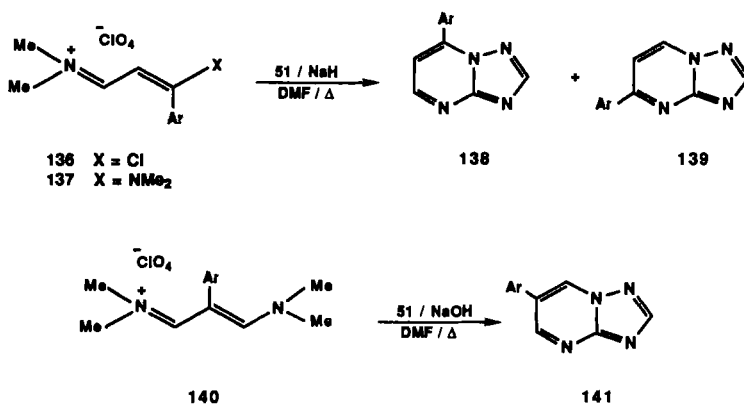
SCHEME 25

anion of **51** can attack the vinylogous iminium salts at two different electrophilic sites followed by removal of X to give the vinylogous iminium salts that cyclized to **138** and **139** (94T12113). Similarly, the 6-substituted triazolopyrimidines **141** were synthesized from 2-substituted vinamidinium salt **140** (95H729) (Scheme 26)

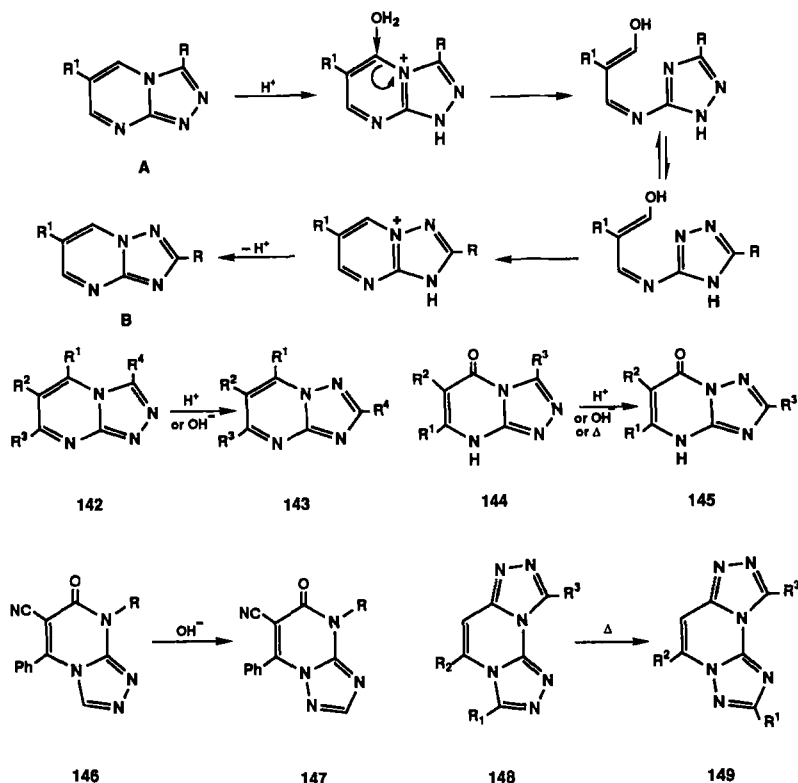
#### 4. Dimroth Rearrangement of 1,2,4-Triazolo[4,3-*a*]pyrimidines

Dimroth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines (**A**) gave the 1,2,4-triazolo[1,5-*a*]pyrimidines (**B**). The triazolopyrimidines with various substituents on the ring, as in **142**, **144**, or **146**, underwent rearrangement to give **143**, **145**, and **147**, respectively, upon treatment with acid, alkali, or triethylamine, or upon fusion (71CB2702; 75JHC1187; 77AJC2515; 83S44; 87T2497; 89H239; 94MI2; 98UP1). bis-1,2,4-Triazolo[4,3-*a*:4',3'-*c*]pyrimidines (**148**) did undergo a thermal rearrangement into system **149** (79AJC1585) (Scheme 27).

Dimroth rearrangement may be considered to be a disadvantage during



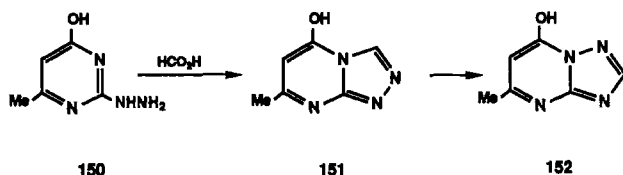
SCHEME 26



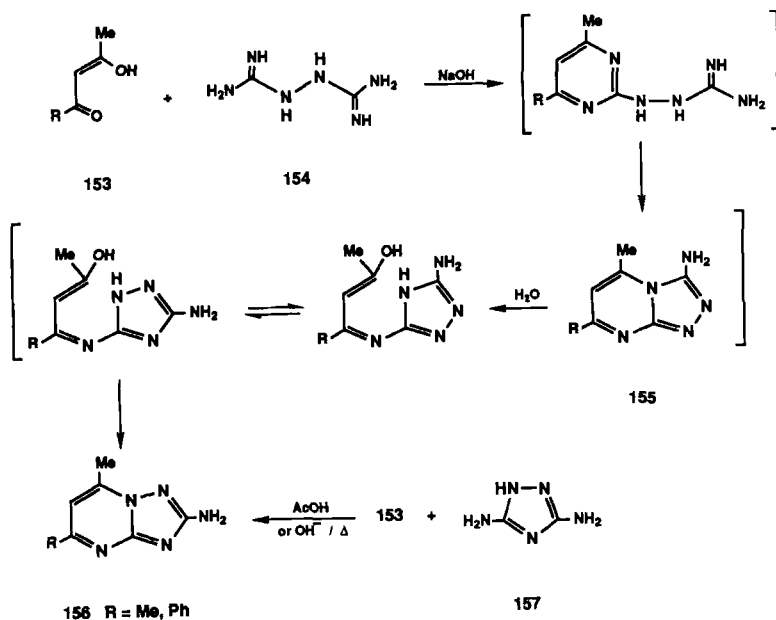
SCHEME 27

the synthesis of the [4,3-*a*] ring, because this ring system cannot be isolated. However, it is advantageous in cases in which the [1,5-*a*] ring system is required. Thus, reaction of the hydrazine **150** with formic acid gave **152** via **151** (53CB1401; 58YZ1395; 59JOC787; 66CB2237) (Scheme 28).

Cyclization of the diamidine **154** with acetyl- or benzoyl-acetone (**153**) gave 1,2,4-triazolo[1,5-*a*]pyrimidine (**156**) via the formation of **155** (66CB2237; 79AP1003). Alternatively, **156** can be prepared by the reaction of **153** with the diaminotriazole **157** (66CB2237) (Scheme 29).



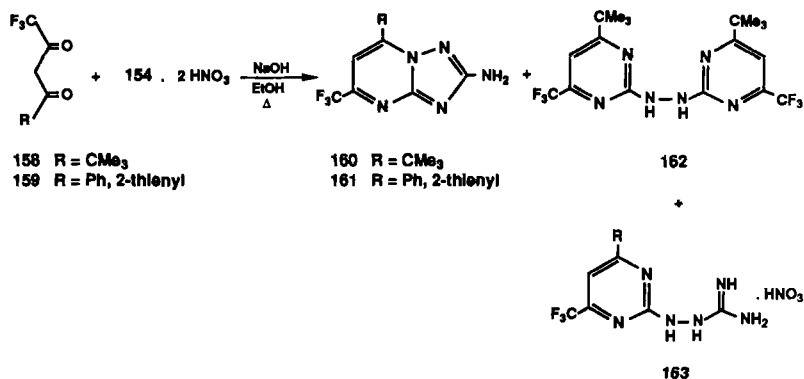
SCHEME 28



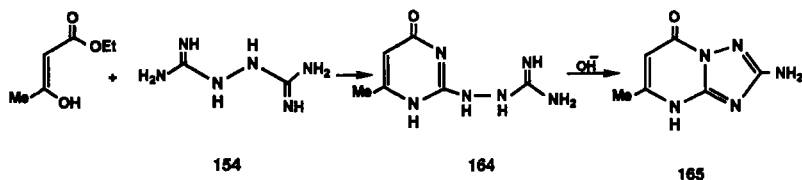
SCHEME 29

Reaction of the trifluoromethyl substituted  $\beta$ -diketone **158** with **154** nitrate gave a mixture of the triazolopyrimidine **160** and the pyrimidine **162**; whereas reaction with the aromatic  $\beta$ -diketones (**159**) gave a mixture of triazolopyrimidines (**161**) and pyrimidines (**163**) (79CZ267; 80AP244) (Scheme 30).

Cyclization of 2-guanidinoamino-6-methyl-1,4-dihydropyrimidin-4-one



SCHEME 30



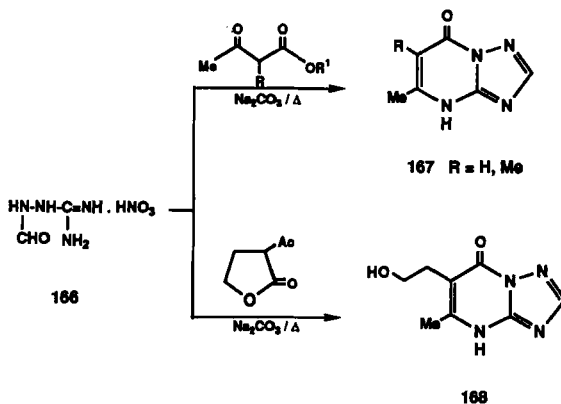
SCHEME 31

(**164**), obtained from the reaction of ethyl acetoacetate with **154** and alkali, gave the aminotriazolo[1,5-*a*]pyrimidinone **165** (79AP816) (Scheme 31).

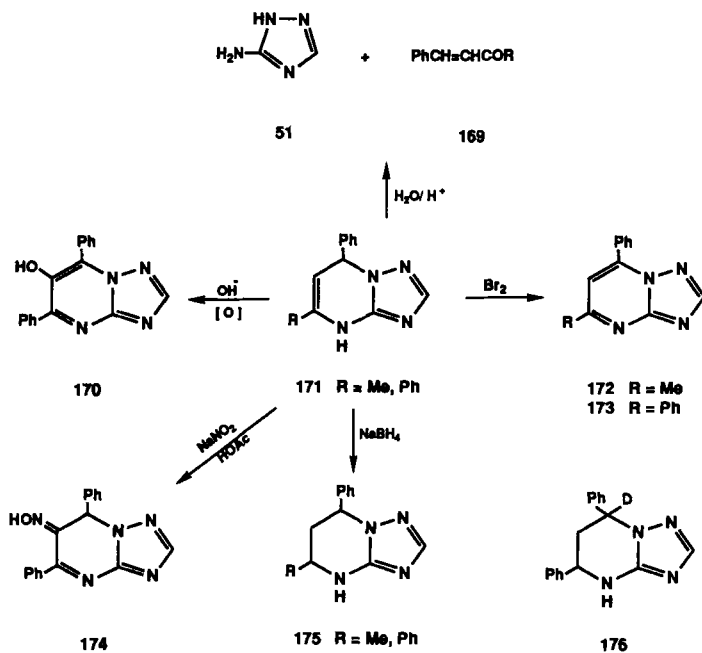
Reaction of the aminoguanidine **166** with either  $\beta$ -ketoesters or  $\alpha$ -acetyl- $\gamma$ -butyrolactone produced the triazolopyrimidine derivatives **167** and **168**, respectively [82JAP(K)57/175193] (Scheme 32).

### 5. Reactivity of Ring Atoms

Hydrolysis of 4,7-dihydrotriazolopyrimidine (**171**) by hydrochloric acid gave the triazole **51** and the unsaturated ketone **169**. Keeping an alcoholic alkali solution of **171** ( $R = \text{Me}$ ) in air afforded 5-methyl-7-phenyltriazolopyrimidine (**172**) and a small amount of resin, but in the case of **171** ( $R = \text{Ph}$ ), both **170** and **173** were separated. Compound **171** ( $R = \text{Ph}$ ) can be dehydrogenated by either  $\text{Br}_2$  or  $\text{SeO}_2$ . The 5-methyl analog **171** ( $R = \text{Me}$ ) is oxidized by  $\text{Br}_2$  but resinsified by  $\text{SeO}_2$ . Nitrosation of **171** ( $R = \text{Ph}$ ) afforded the 6-oximo derivative **174**. Reduction of **171** with sodium borohydride gave the tetrahydro derivative **175** (90KGS1362), which can be *N*-methylated (94KGS981). The 7-deuteriotetrahydrotriazolopyrimidine **176** was prepared by condensation of the amine **51** with



SCHEME 32

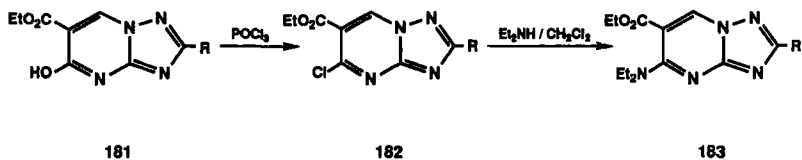
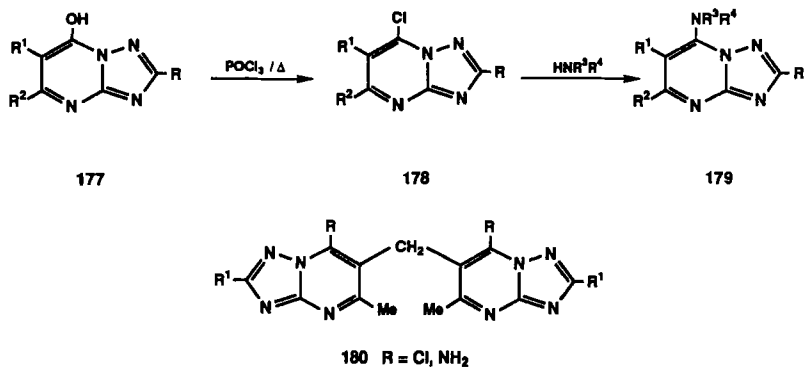


SCHEME 33

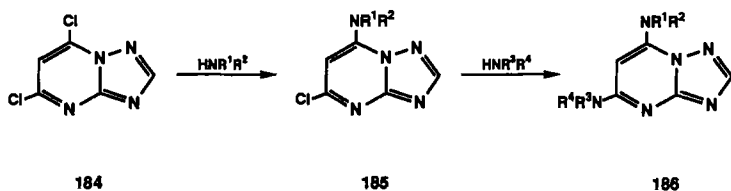
**$\beta$ -deuterochalcone (90KGS1362).** Aromatization of 2,5,7-trisubstituted 4,7(6,7)dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines can be achieved by the action of NBS/MeOH (88KGS229; 89MI2) (Scheme 33).

Chlorination of 7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidines (**177**) by POCl<sub>3</sub> gave the 7-chloro derivative **178** [85GEP3338292; 88GEP3702322, 88IJC(B)825; 90EGP280006], whose amination with a variety of primary and secondary amines including heterocyclic compounds gave **179** [80FRP2448542; 86JAP(K)61/57587; 88EGP255734, 88EGP256327, 88EGP256328; 90EGP280006; 92MI4; 95PHA33]. The bis(7-amino-5-methyl-2-substituted 1,2,4-triazolo[1,5-*a*]pyrimid-6-yl)methanes (**180**, R = NH<sub>2</sub>) were similarly prepared (90EGP276284). Chlorination of 5-hydroxytriazolopyrimidine (**181**) with POCl<sub>3</sub> gave the chloro derivative **182**, which with Et<sub>2</sub>NH in CH<sub>2</sub>Cl<sub>2</sub> gave **183** [92JAP(K)04/99775] (Scheme 34).

The 5- and 7-positions of the 1,2,4-triazolo[1,5-*a*]pyrimidine ring are very reactive toward nucleophilic substitution, the 7-position being the more reactive. Thus, the 7-substituted and 5,7-disubstituted triazolo[1,5-*a*]pyrimidines **185** and **186** were prepared by the reaction of 5,7-dichloro-1,2,4-triazolo[1,5-*a*]pyrimidine (**184**) with amines or hydrazines [81KFZ31; 88IJC(B)825; 91PHA184] (Scheme 35).



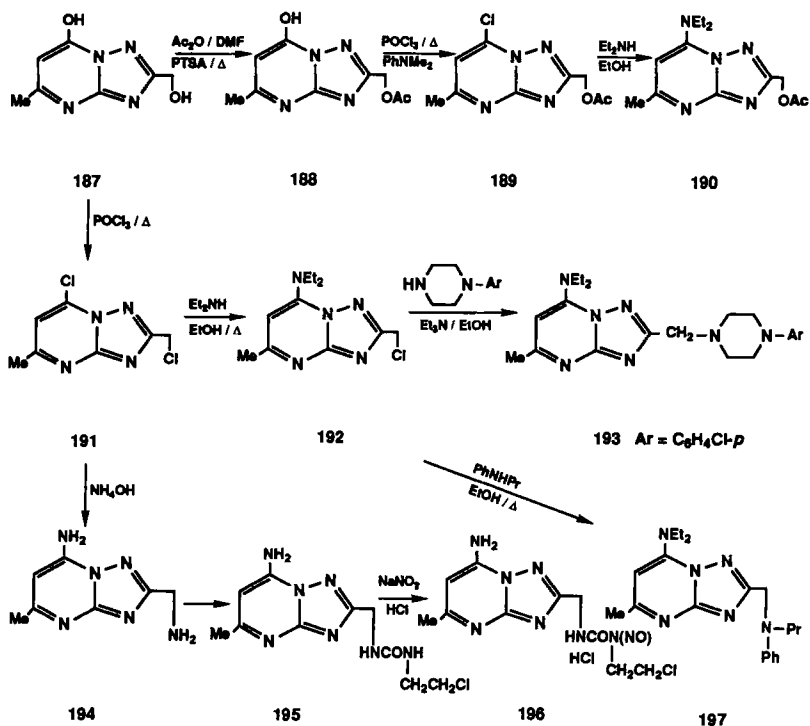
SCHEME 34



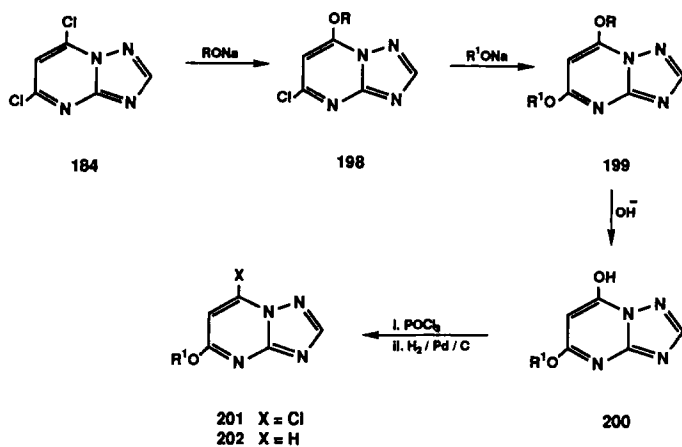
SCHEME 35

To protect the hydroxymethyl group in **187** from chlorination, its acetylation was done to give **188**, followed by chlorination to give **189**, which upon treatment with Et<sub>2</sub>NH finally gave **190** [90EGP280006, 90JAP(K)02/212488]. Reaction of **187** with POCl<sub>3</sub> gave the dichloro derivative **191**, whose subsequent reaction with Et<sub>2</sub>NH gave **192** and then with PhNHPr afforded **197** (82JAP82/35592; 83MIP1) and with 1-(4-chlorophenyl)piperazine yielded **193** [91JAP(K)03/118383]. Aminolysis of **191** with NH<sub>4</sub>OH gave **194**, whose reaction with Cl(CH<sub>2</sub>)<sub>2</sub>NHCOCl gave **195**, which with nitrous acid gave the hydrochloride **196** (Scheme 36).

The chlorine atoms at positions 5 and 7 can be displaced by alkoxide ions selectively. Thus, **184** gave **198** and then **199**, which by the action of alkali formed **200**. Chlorination of **200** with POCl<sub>3</sub> gave **201**, which upon hydrogenation gave **202** (63CPB845) (Scheme 37).



SCHEME 36



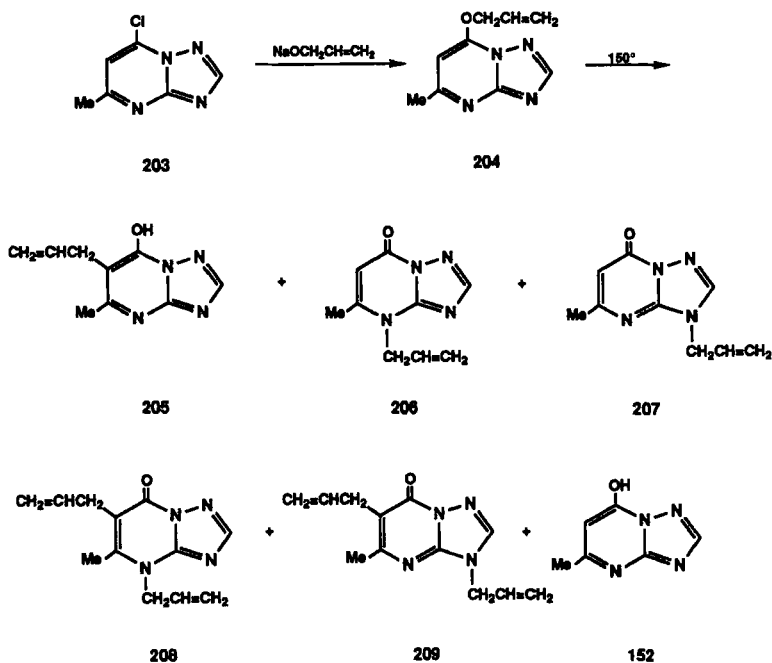
SCHEME 37



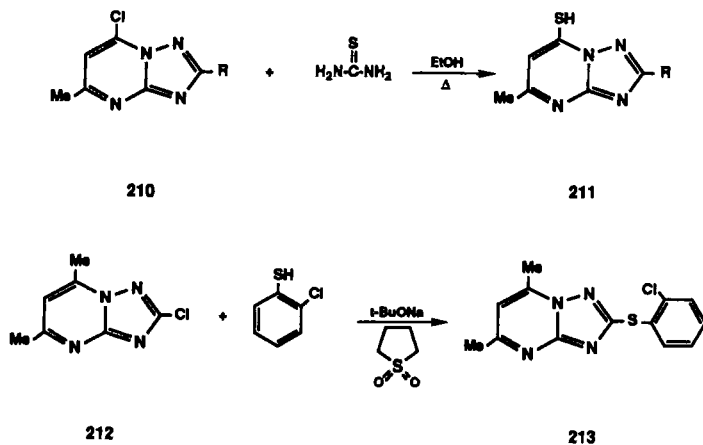
Displacement of the chlorine atom in **203** with sodium allyloxide in allyl alcohol gave 7-allyloxy-1,2,4-triazolo[1,5-*a*]pyrimidine (**204**). This was followed by a thermal Claisen rearrangement to **205–209** in addition to **152**. Allylation of **152** with allyl bromide gave the two allylated products **206** and **207** (63CPB851) (Scheme 38).

Reaction of the chloro derivative **210** with thiourea gave the thio derivative **211** [88IJC(B)825]. Displacement of the chlorine in **212** with 2-chlorothiophenol formed 2-(arylthio)-1,2,4-triazolo[1,5-*a*]pyrimidine (**213**) (89EUP337232) (Scheme 39).

The cyanotriazolopyrimidinone **214** was chlorinated with  $\text{POCl}_3$ /*N,N*-diethylaniline and subsequently cyclocondensed with ethyl thioglycolic ester to give **215**, whose amino group was acetylated with  $\text{Ac}_2\text{O}$  (91OPP413). On increasing the amount of diethylaniline in is chlorination, major product **221** was formed in addition to **220** (91KGS281). Chlorination of 7-hydroxy-6-nitrotriazolopyrimidine derivatives **216** with  $\text{POCl}_3$  in the presence of *N,N*-dialkylanilines gave **217** (88EGP255735) together with **218** as a side product, which upon heating with benzylamine in EtOH or DMF led to an unusual synthesis of 1-hydroxy-2-phenyl-5-benzylimino [4-(dialkylamino)phenyl]methylimidazole (**219**). Use of a twofold excess of



SCHEME 38



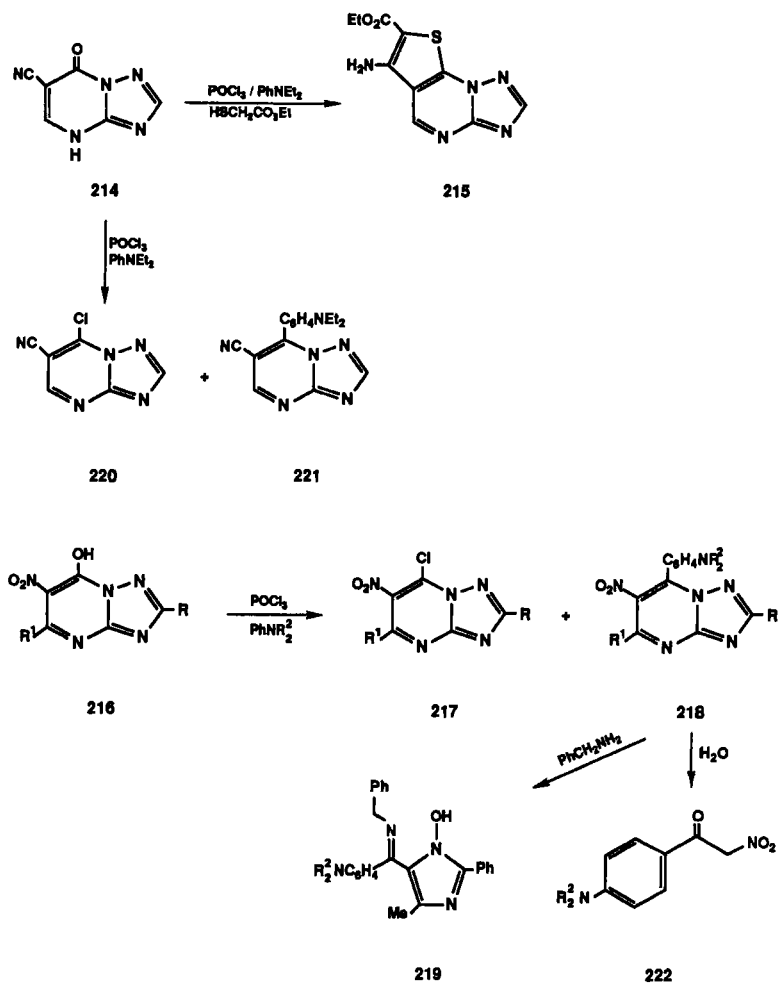
SCHEME 39

dialkylaniline made it possible to increase the yield of **218** to make it the only isolated product (90ZC170; 91ZOR1100; 93MC213). The arylation of **216** was independent of the nature of the substituents on the triazole and pyrimidine rings, but the presence of a nitro group in position 6 is essential. The nitroaryltriazolopyrimidines (**218**) underwent destruction with water to give nitroacetophenones (**222**) (91ZOR2461; 92KGS1546) (Scheme 40).

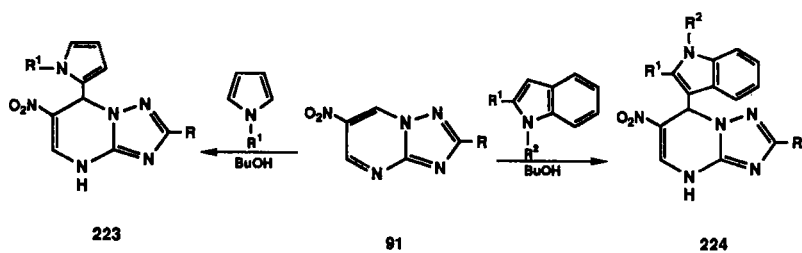
The C-7 adducts **223** and **224** were formed by the reaction of pyrroles or indoles, respectively, with 6-nitrotriazolopyrimidines (**91**) in butanol (85KGS1266; 86KGS1544; 88KGS1251; 90KFZ41). When the reaction was carried out in an alkaline solution, the pyrrolyl- and indolyltriazolopyrimidinium salts were obtained (90KFZ41) (Scheme 41).

Reaction of **91** with malononitrile and ethyl cyanoacetate gave 9-imino(oxo)-7-nitro-4,9-dihydrotriazolopyridopyrimidine (**226**). The triazolylaminonitropyridines (**225**) ( $R^1 = \text{CO}_2\text{Et}$ ) can be isolated and transformed to **226** (90KGS1632, 90S713; 91KGS256; 93ZOR789). Malononitrile or ethyl cyanoacetate provided the C-C-N fragment for the pyridine ring. By using  $^{15}\text{N}^{13}\text{CCH}_2\text{CO}_2\text{Et}$  in this reaction, its participation as a 1,3-bifunctional reagent was established (Scheme 42).

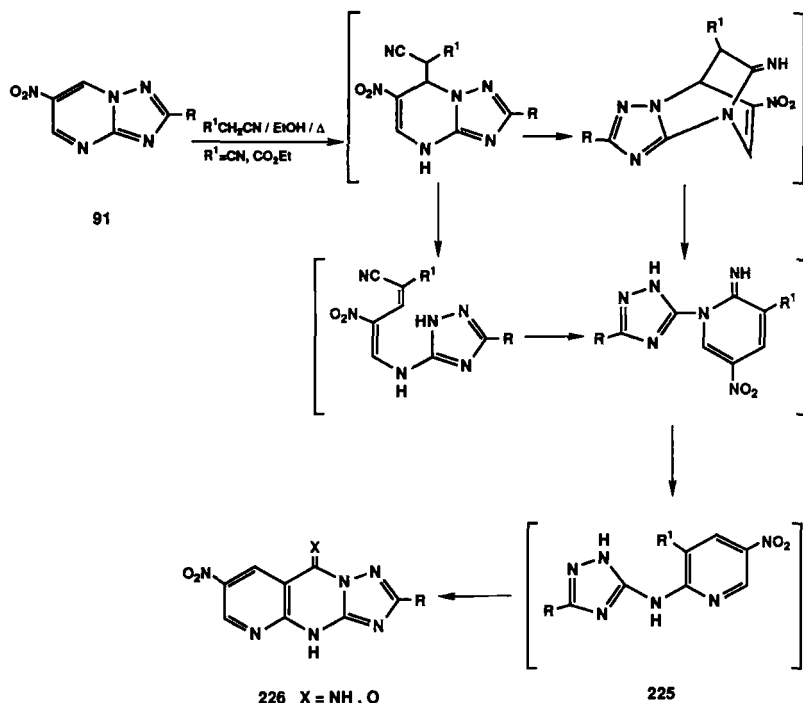
Nucleophilic additions of the acetonide anion to 6-nitrotriazolopyrimidines (**91**) gave  $\sigma$ -adducts (**227**), whose acidification afforded the dihydro adduct **228** (93KGS807). Direct addition of cyclic  $\beta$ -diketones such as dime-done and indanedione to **91** led to the adducts **229** and **230**, respectively (93ZOR622). The reactivity of this class of compounds with respect to charged and uncharged nucleophiles is determined by their aromatic character and the deficit of electron density in the pyrimidine ring, and the di-



SCHEME 40



SCHEME 41



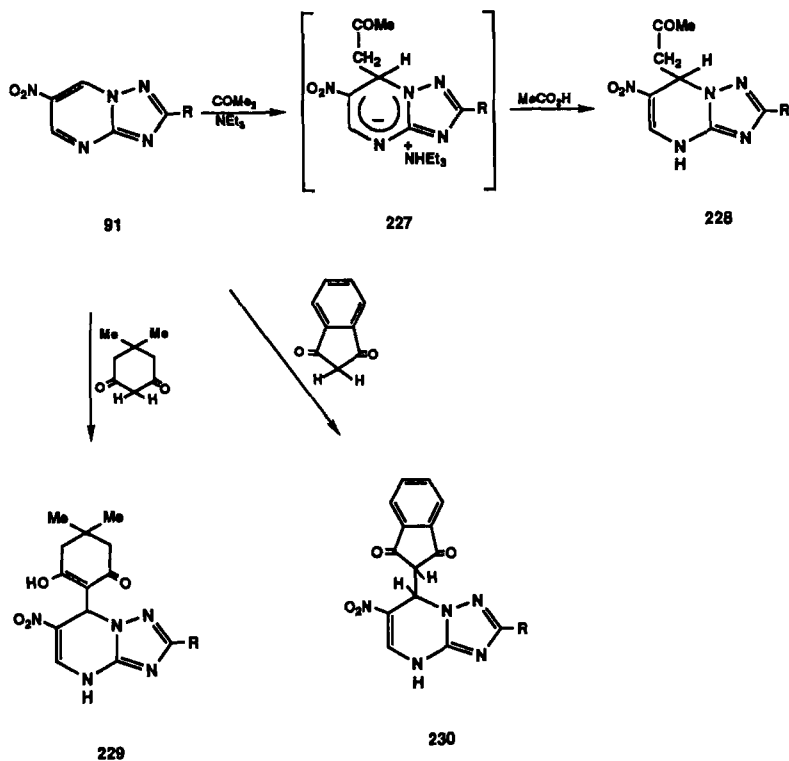
SCHEME 42

rection of nucleophilic attack is determined by the overall charge on fragments of the valance-bonded atoms (93KGS807) (Scheme 43).

Reaction of triazolopyrimidine **152** with *N*-acyltrichloroacetalimine (**231**) gave the trisubstituted triazolopyrimidine **232** and not the *O*-substituted derivative (91JPR661).

The introduction of a carbaldehyde group at position 6 was achieved by applying the Vilsmeier–Haak reaction to **233** to give **234** (89EGP264439). Nitration of triazolopyrimidine **235** afforded the nitro derivative **236** (90ZC170) (Scheme 44).

Alkylation of 7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine (**237**) with EtI in DMF gave the 4-*N*-ethyl derivative **240** as a major product, together with a small amount of the 3-*N*-ethyl derivative **242** [63CPB129; 67JCS(C)503]. Similarly, **238** with an excess of ethyl iodide in dimethylformamide-hexamethylphosphoric triamide (DMF/HMPT) afforded **241** and **243** as the major and minor products, respectively [80JCS(P1)1347]. Alkylation of 4,7-dihydrotriazolopyrimidines **244** with dimethyl sulfate or MeI in alcoholic alkali afforded the 4-*N*-methyl derivatives **245** (90KGS1362). Methylation of **216** gave a mixture



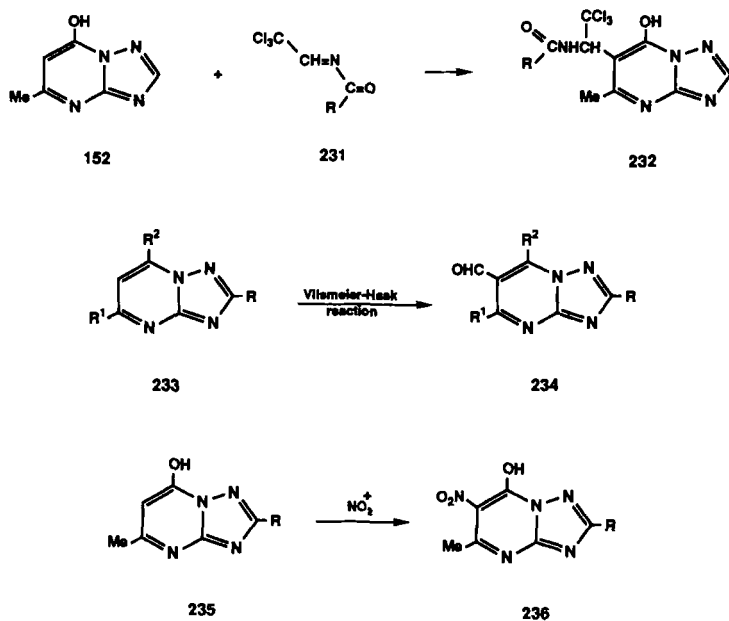
SCHEME 43

of 3-*N* and 4-*N*-methyl derivatives (93ZOR629). The ester **238** was hydrolyzed in acidic media to the free acid **239** [80JCS(P1)1347] (Scheme 45).

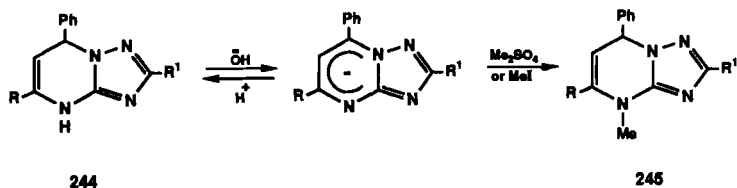
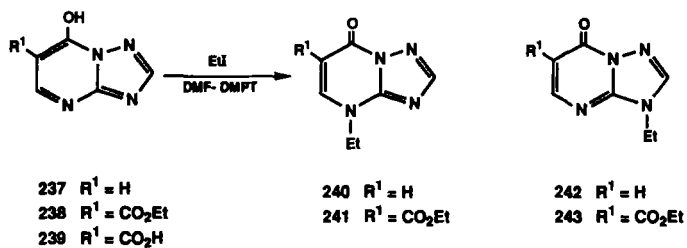
Reaction of 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**246**) with phenacyl bromide gave the triazolopyrimidinium salt **247** (85JCS(P1)2333; 85TL1321). Treating **247** with one equivalent of triethylamine gave the ylide **248**, whose thermolysis in acetonitrile gave *N*-cyano-*N*-phenacylaminopyrimidine (**249**), but when **247** was treated with two equivalents of triethylamine, the 2-iminooxazoline **250** was formed, which was also obtained from **249** by further treatment with another equivalent of triethylamine (Scheme 46).

Alkylation of **251**, having a 2-amino group, with a phenacyl halide gave the triazolopyrimidinium salts **252** (80KGS1695), which upon treatment with base gave the mesoionic imidazotriazolopyrimidines **253** (86UKZ200) (Scheme 47).

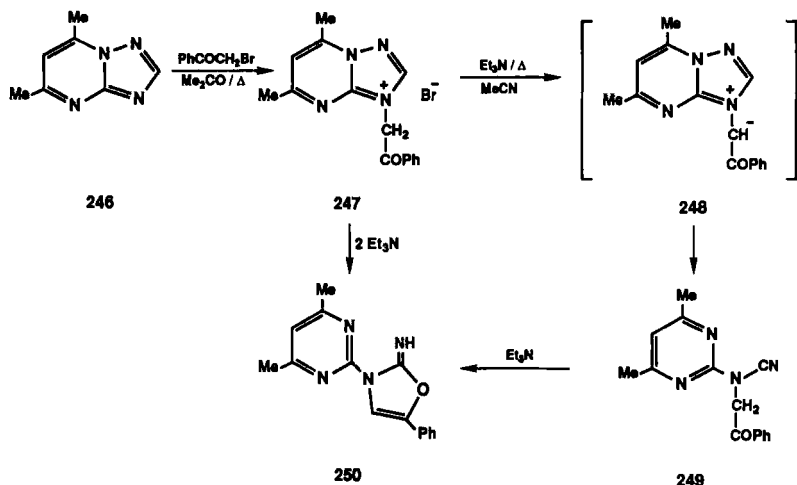
Coupling of **99** with the diazonium salt of 4-aminoantipyrene gave antipyrinylazoanilineoxotriazolopyrimidine (92JSC165).



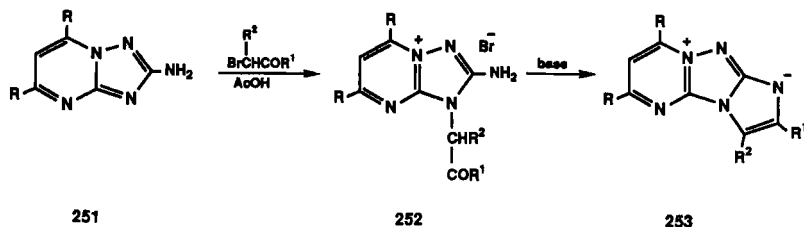
SCHEME 44



SCHEME 45



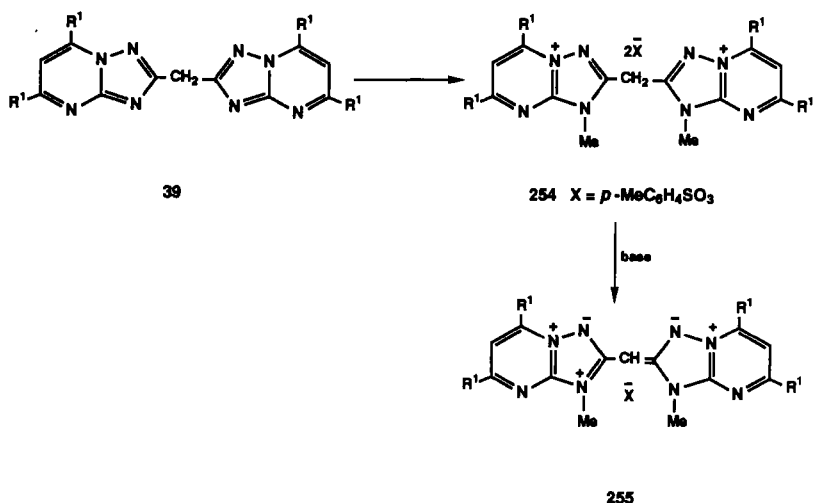
SCHEME 46



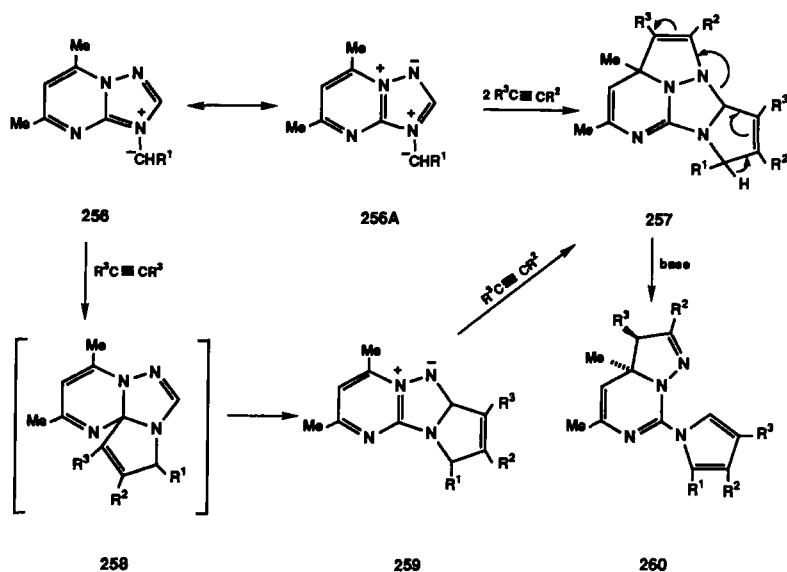
SCHEME 47

The bis(triazolopyrimidyl)methanes **39** were quaternized with methyl *p*-toluenesulfonate to give **254**, whose treatment with base gave the mesoionic methine dyes **255** (82UKZ79). The methylene group of **39** was active to be condensed with aldehydes (Scheme 48).

Reaction of triazolopyrimidinium ylides (**256**) with active acetylenes gave the 1:2 adducts **260**. The formation of **260** may occur in two ways; the shortest pathway consists of the double 1,3-dipolar cycloaddition of the diylide **256A** with two molecules of the acetylene at two different sites to form the tetracyclic adduct **257**, followed by ring opening under basic conditions to give **260**. The second pathway consists of cycloaddition between the ylide carbanion of **256** and the bridged carbon C-4 to form the 1:1 adduct **258**, which isomerizes to the more stable compound **259**, which may be formed directly by the cycloaddition at the ylide carbanion and C-2. The second cycloaddition afforded the 1:2 adduct **257** [87JCS(P1)2531] (Scheme 49).



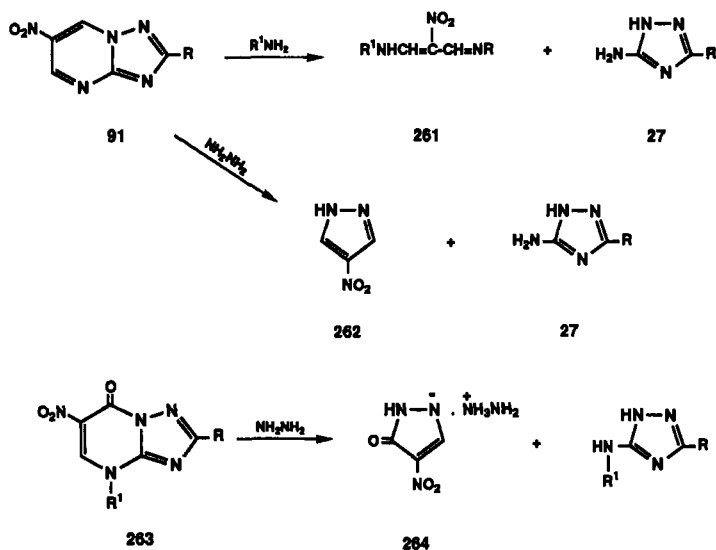
SCHEME 48



SCHEME 49

The pyrimidine ring in 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines (**91**) underwent a ring transformation by amines to give **261** and the aminotriazole **27**, and by hydrazine to give 4-nitropyrazole (**262**) and **27** (89KGS278; 91ZOR1100). Heating 6-nitro-dihydrotriazolopyrimidinones (**263**) with hy-





SCHEME 50

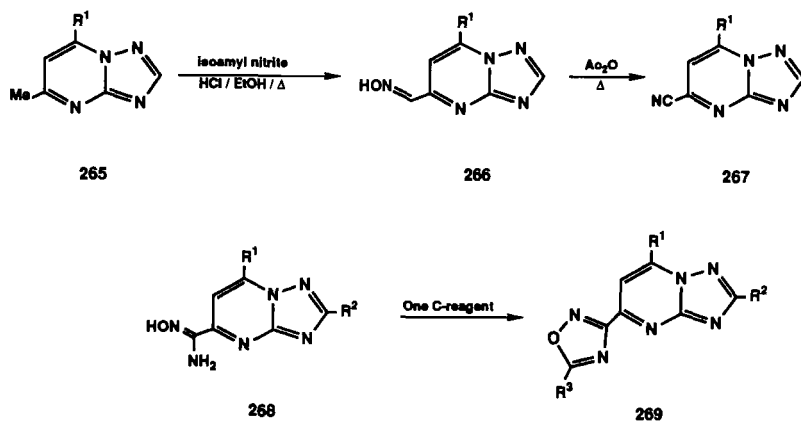
drazine hydrate resulted in a ring cleavage and contraction to give the nitropyrazolone hydrazinium salt **264** and 5-substituted aminotriazole (91KGS665) (Scheme 50).

Synthesis of copper and zinc complexes of 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine has been reported [93AX(C)1902; 94AX(C)510]. Reaction of copper(II) thiocyanate with 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**1**) gave three different complexes: two isomers of  $[Cu(NCS)_2L_2]_2$  and  $Cu(NCS)_2L_2 \cdot H_2O$  (84IC2803). The mononuclear complexes, bis(thiocyanato-*N*)bis(6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine-*N*-3)copper(II) and the polynuclear pseudo-layered complexes, bis(thiocyanato-*N*)bis(5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine-*N*-3)copper(II) were prepared (89POL2313).

## 6. Reactivity of Substituents

The methyl group at position 5 in triazolopyrimidine **265** reacted with isoamyl nitrite to give the oxime **266**, which was dehydrated to the carbonitrile **267** (89EGP269149). Cyclization of the respective amidoxime **268** with acid chlorides, acid anhydrides, chloroformate esters and *o*-carboxylic acid esters gave the oxadiazolyl derivatives **269** (90EGP282009) (Scheme 51).

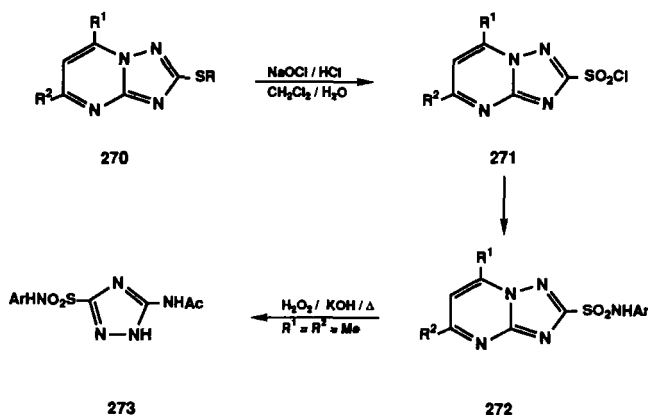
Hypochlorite oxidation of 2-thio(or benzylthio)triazolopyrimidines (**270**)



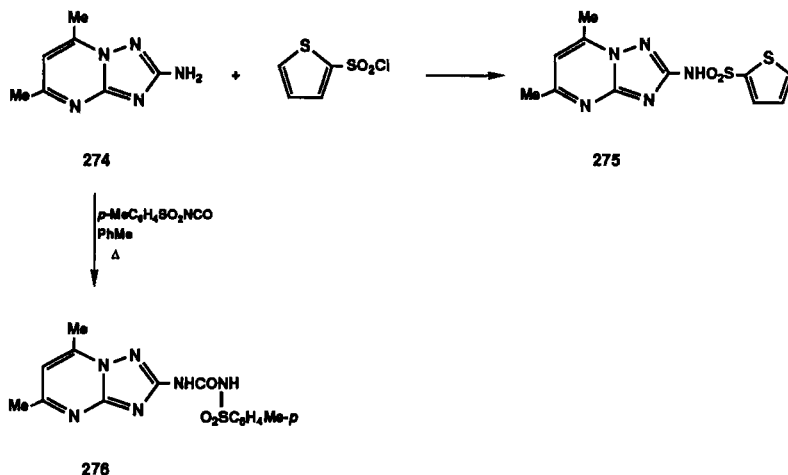
SCHEME 51

in a two-phase solvent system gave the 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonyl chlorides **271** (85EUP142811; 91EUP343624), whose condensation with aromatic or heterocyclic amines or their *N*-trimethylsilyl derivatives gave the sulfonamides **272** (85EUP142152; 88GEP3627411; 89USP4822404; 90EUP375076, 90EUP378508, 90USP4910306; 91EUP343624). Hydrogen peroxide oxidatively cleaved **272**, which has electron-withdrawing substituents on the sulfonamido group, to form the triazolesulfonamides (**273**) (85USP4818273; 87EUP244847) (Scheme 52).

Reaction of **274** with 2-thiophenesulfonyl chloride gave **275** (86EUP 150974) and with *p*-toluenesulfonyl isocyanate gave the sulfonyl urea **276**



SCHEME 52



SCHEME 53

(89USP4866063). The amino group can also be acylated and tosylated (91MI1; 93MI1) (Scheme 53).

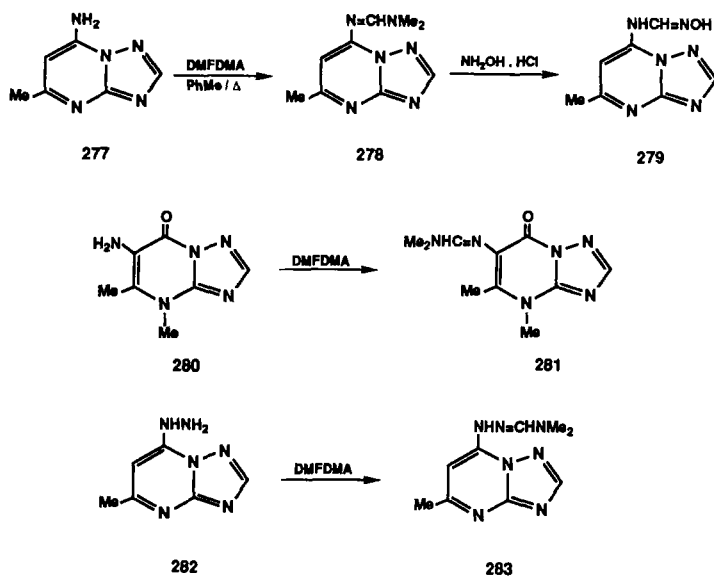
Condensation of amine **277** with dimethylformamide dimethylacetal (DMF/DMA) gave *N,N*-dimethyl-*N'*-(5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-yl)formamidine (**278**), whose reaction with hydroxylamine gave the formamidoxime **279** (89EGP264438; 90ZC320). The amine **280** and the hydrazine **282** can be transformed into the amidine **281** and amidrazone **283**, respectively (90ZC320) (Scheme 54).

Reaction of 5-hydrazinotriazolopyrimidines (**284**) with carbon disulfide gave **287** and with ethyl chloroformate gave **285**, whose cyclization with pyridine led to bis(1,2,4-triazolo[1,5-*a*:4,3-*c'*])pyrimidines (**286**) (91PHA184) (Scheme 55).

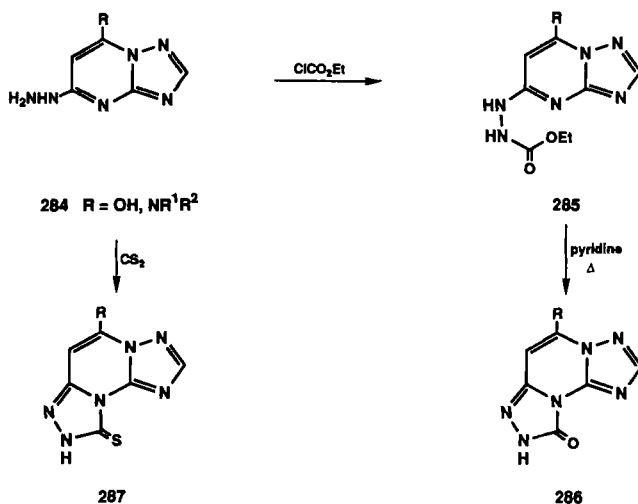
Condensation of 2-chloromethyl-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidin-7-ol (**288**) with lithium 2,2-diphenyl-1,3-benzodioxole-5-sulfinate (**289**) afforded the sulfonylated product **290**, which was condensed with 7-aminocephalosporanic acid to give **291** (93EUP544166) (Scheme 56).

## 7. Physicochemical Data

Chemical reactivity and NMR spectroscopy suggested that the triazolopyrimidines with bridgehead nitrogens are planar and possess a high degree of aromatic character (80PAC1611). The aromaticity of 6-nitrotriazolopyrimidines was found to be more sensitive to substituent effects than the  $\Delta\bar{N}_s$  index (91ZOR144). The tautomeric equilibrium of the

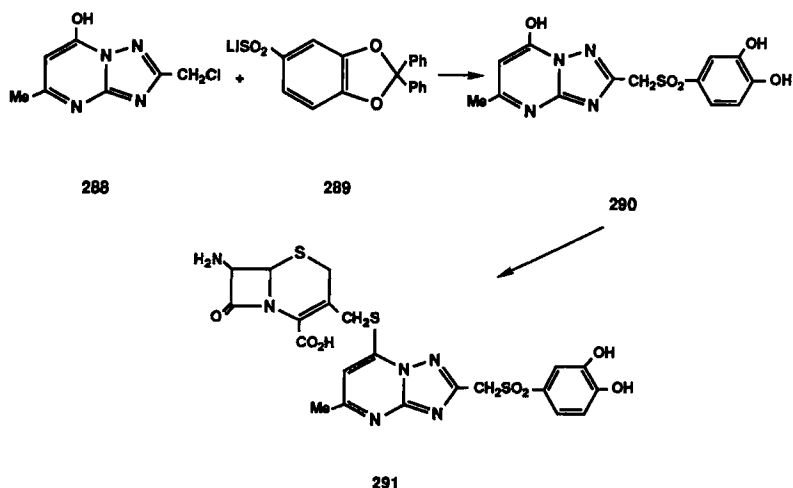


SCHEME 54



SCHEME 55

dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine derivative **292** was shifted to the imine **292B** in acetonitrile, acetone, benzene, and chloroform. The concentration of **292A** increased in proton-accepting solvents such as dimethyl sulfoxide (DMSO) and pyridine as a result of specific and nonspecific solva-

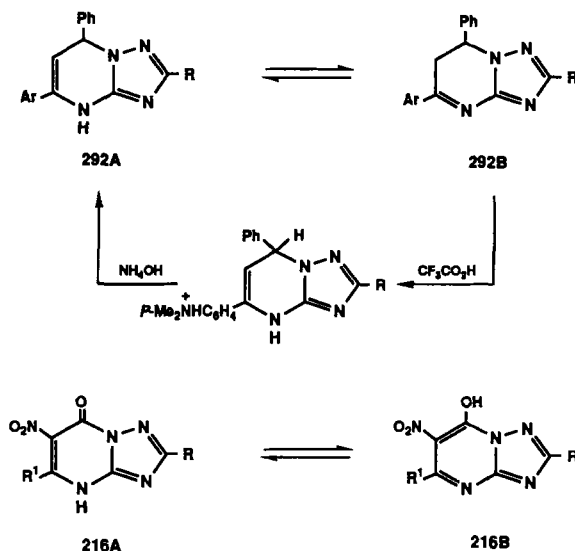


SCHEME 56

tion effects. The kinetics of tautomerization of **292A/292B** in methanol and chloroform have been reported (88KGS229; 91KGS245). X-Ray analysis demonstrated that **292** (Ar = C<sub>6</sub>H<sub>4</sub>NMe<sub>2</sub>-*p*) has the 6,7-dihydro structure **292B** in the solid state; its isomerization into the 4,7-dihydro species **292A** has been achieved by the action of CF<sub>3</sub>CO<sub>2</sub>H followed by neutralization with aqueous ammonia via the protonated dimethylamino group (92KGS933). The tautomerism of triazolopyrimidinones (**216**) was studied by <sup>1</sup>H and <sup>13</sup>C NMR, mass spectrometry, and X-ray analysis (93ZOR629).

An increase in the bulk of the substituent at C-7 in 5,7-disubstituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines led to relative stabilization of the enamine tautomer. NMR spectroscopy was used to show that the enamine form is predominant in DMSO in contrast to that in CHCl<sub>3</sub>. X-Ray diffraction analysis of 7-*t*-butyl-5-(4-methoxyphenyl)-4,7-dihydro triazolopyrimidine showed that the introduction of a *t*-butyl group into the dihydropyrimidine ring led to a significant loss of planarity (89KGS 1000; 91KGS1539; 93KGS481, 93KGS1353, 93KGS1357, 93KGS1433) (Scheme 57).

C-Alkyl-1,2,4-triazolo[4,3-*a*]pyrimidines are distinguished from their respective [1,5-*a*]isomers by their UV absorption at longer wavelength. The UV spectra (at pH 2 and pH 10) have been used to differentiate the isomeric 5- and 7-hydroxy-1,2,4-triazolopyrimidines; this differentiation may be confirmed by the IR stretching frequency of the CO group. The isomeric *N*-alkyl-1,2,4-triazolopyrimidines are more readily distinguished by their IR spectra (68T2839). <sup>1</sup>H and <sup>13</sup>C NMR and UV spectroscopy have been



SCHEME 57

utilized to investigate the structure **226** (94KGS235).  $^{13}\text{C}$ -chemical shift values for compounds **238**, **241**, and **243** have been assigned [80JCS(P1)1347].

The ring proton chemical shifts ( $\delta$  values) of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives are in the order  $\text{H-7} > \text{H-5} > \text{H-2} > \text{H-6}$  (64CPB204). The charge densities determined from proton chemical shifts showed a remarkably good correspondence with the charge distributions calculated by the simple Hückel Molecular orbital (HMO) method (64CPB204). HMO calculations for all possible tautomeric forms of the isomeric triazolopyrimidin-5(7)-ones were also performed (88M341).

The equilibrium geometry of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine was calculated by the semiempirical modified neglect differential overlap (MNDO) method. The dihydropyrimidine ring exhibits high conformational mobility. The change in the energy occurring in the transition of the molecule to the boat conformation with an angle between the planar fragment of  $\pm 20^\circ$  does not exceed  $1 \text{ Kcal} \cdot \text{mol}^{-1}$ . The mobility of the dihydro ring increases as the interaction between the  $\pi$ -system of the azole ring and the  $\text{C}=\text{C}$  bond of the pyrimidine ring decreases (94IZV1418). The introduction of substituents into the saturated C-7 atom leads to the transition of the dihydropyrimidine ring to an irregularly flat-ended boat conformation (94IZV1394).

The monoclinic crystal structure of 5,7-diphenyl-7-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine showed the presence of steric strain and a

twisted conformation (93IZV1912). The structure of **241** was confirmed by an X-ray analysis [80JCS(P1)1347].

The crystal structure of diaquotris(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-*N*-3)copper(II) perchlorate dihydrate (dmtp) indicated that it is triclinic and consists of  $[\text{Cu}(\text{dmtp})_3(\text{H}_2\text{O})_2]^{2+}$ -coordinated cations,  $\text{ClO}_4^-$  anions, and interstitial water molecules. The copper atom is coordinated by three nitrogen atoms of the triazolopyrimidine ligands. The copper polyhedron is a trigonal bipyramid. This compound is the first such complex with a  $\text{ClO}_4^-$  anion and the first mononuclear complex involving three dmtp ligands whose crystal structure has been solved by X-ray diffraction [93AX(C)1902]. The structure of the complex bis( $\mu$ -bromo)bis[bromobis(dmtp)copper(II)]dihydrate, which consists of dimeric molecules,  $[\text{Cu}(\text{dmtp})_2\text{Br}_2]_2$ , whose copper atoms are bridged by bromine ligands, has been determined by single-crystal X-ray diffraction. The geometry at copper is a distorted trigonal bipyramid, with bromine atoms occupying equatorial positions and N-3-coordinated dmtp ligands in apical positions (94IC5477).

The IR, UV, ESR, single-crystal X-ray diffraction, and magnetic susceptibilities of  $[\text{Cu}(\text{NCS})_2(\text{dmtp})_2]_2$ ,  $\text{Cu}(\text{NCS})_2(\text{dmtp})_2 \cdot \text{H}_2\text{O}$ , the mononuclear complexes, bis(thiocyanato-*N*)bis(6-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine-*N*-3)copper(II), and the polynuclear pseudo-layered complexes, bis(thiocyanato-*N*)bis(5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine-*N*-3)copper(II) were reported (84IC2803; 89POL2313).

## 8. Nucleoside Analogs

The importance of this group arises from the fact that the 1,2,4-triazolo[1,5-*a*]pyrimidine is a purine in which N-1 and C-5 atoms are interchanged. Coupling of the trimethylsilyl derivative of 1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**293**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**296**;  $\text{R}^1 = \text{Bz}$ ) in acetonitrile led to the formation of two blocked isomeric nucleosides, which upon reaction with methanolic ammonia at room temperature gave the crystalline nucleosides, 3-( $\beta$ -D-ribofuranosyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (**297**;  $\text{R} = \text{H}$ ) and the N-4 isomer **298** (59CPB907; 71JHC237). Halogen in 5-chloro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one has been predicted to deactivate its neighboring nitrogen in a glycosylation reaction, thereby producing the N-3 glycosyl derivative. Thus, condensation of the trimethylsilyl derivative **294** with **296** ( $\text{R}^1 = \text{Ac}$ ) in acetonitrile at room temperature furnished only one isolable blocked nucleoside, whose deacetylation gave **297** ( $\text{R} = \text{Cl}$ ), and subsequent dehalogenation with palladium on carbon afforded **297** ( $\text{R} = \text{H}$ ). A similar glycosylation of **295** gave

the N-3-blocked nucleoside, which on subsequent deacetylation gave **297** (*R* = Me). The site of glycosylation of these unnatural nucleosides has been determined unequivocally by a combination of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic methods. The anomeric configurations have been established by  $^1\text{H}$  NMR analysis of the 2',3'-*O*-isopropylidene derivatives (57MI1; 59 JCP11; 61CPB801; 74JOC1256, 74JOC3226). Isopropylidenation of the 5-chloronucleoside **297** (*R* = Cl) with 2,2-dimethoxypropane and acetone in the presence of perchloric acid gave **300** (73JHC1069; 74TL129). Treatment of **300** with *p*-toluenesulfonyl chloride in pyridine furnished the 5'-*O*-*p*-toluenesulfonyl derivative **301**, which upon treatment with DMSO or acetyl acetone did not produce the anticipated cyclonucleoside **304**. This observation indicates that either **297** (*R* = Cl) has the  $\alpha$ -configuration (51JCS2952) or N-4 is not nucleophilic enough to displace the 5'-tosylate. However, dehalogenation of **301** with palladium on carbon gave **303**, which when heated in DMSO effected the formation of the cyclonucleoside **305**, thereby establishing the anomeric configuration of **297** as  $\beta$ . Treatment of **297** (*R* = Cl) with hydrazine gave the rearranged product **299**, whereas treatment with liquid ammonia gave the ring-opened product **302** (74JOC1256, 74JOC3226) (Scheme 58).

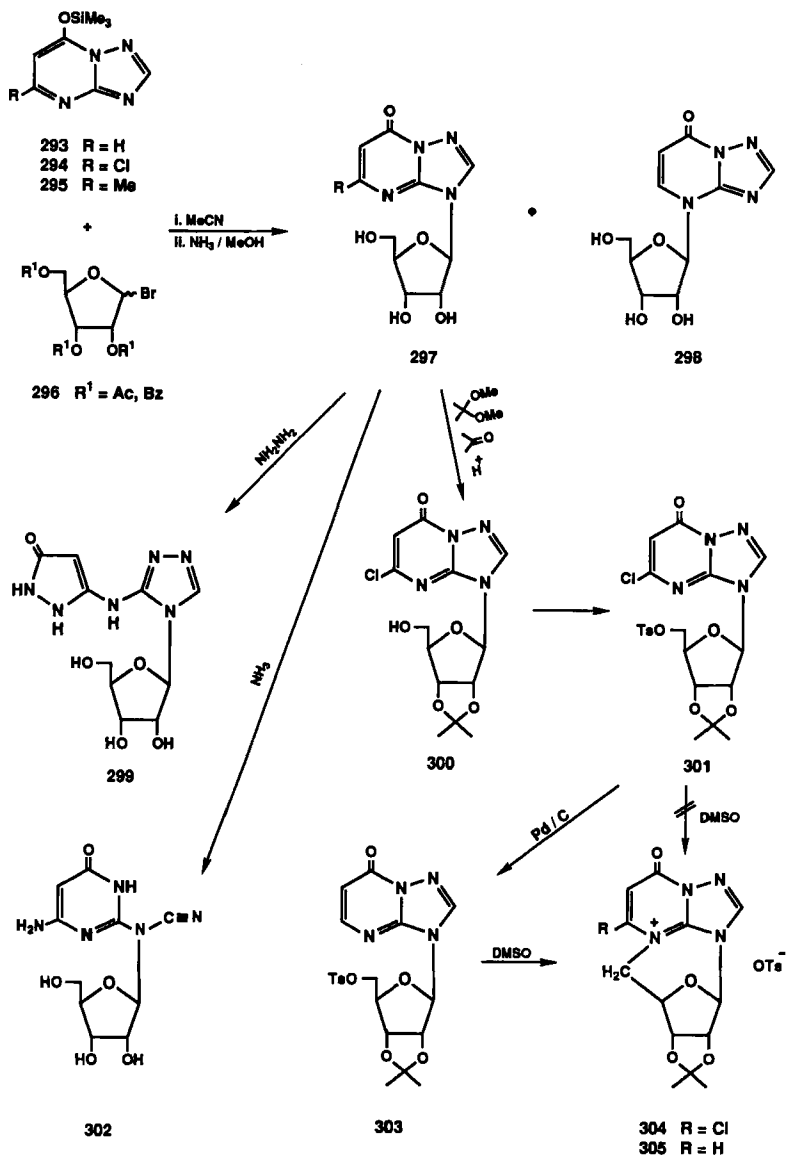
Fusion of the base **306** with 1,2,3,5-tetra-*O*-acetyl- $\beta$ -D-ribofuranose (**307**) in the presence of  $\text{I}_2$  catalyst gave a mixture of nucleosides (**308–311**) in low yields. Better yields were obtained by thionation with phosphorus pentasulfide of the oxo derivatives, 4-(2',3',5'-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one (**312**) and its N-3-isomer **313** (77MI1), to afford **308** and **310**, respectively. Subsequent deacetylation by the action of sodium methoxide or methanolic ammonia afforded **315** and **316**. Amination of **308** gave **314** (78MI1) (Scheme 59).

Glycosylation of *N,O*-bis(trimethylsilyl)-7-aminotriazolopyrimidine (**318**) with **296** gave **319** after deacetylation, whereas glycosylation of **317** with **296** followed by deacetylation yielded the 4- $\beta$ -D-ribofuranosyl derivative **320**, which upon acid hydrolysis gave **321**. The site of glycosylation has been determined by NMR spectral comparisons of the H-2 chemical shifts (74JOC1256) (Scheme 60).

Dimroth rearrangement has taken place in the *C*-nucleoside series, whereby the reaction of ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**322**) with 2-hydrazinopyrimidine did not afford the 3-substituted 1,2,4-triazolo[4,3-*a*]pyrimidine **323**, but gave 2- $\beta$ -D-ribofuranosyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**324**). Upon treatment of the latter with methanolic ammonia, the free *C*-nucleoside **325** was obtained (89MI3) (Scheme 61).

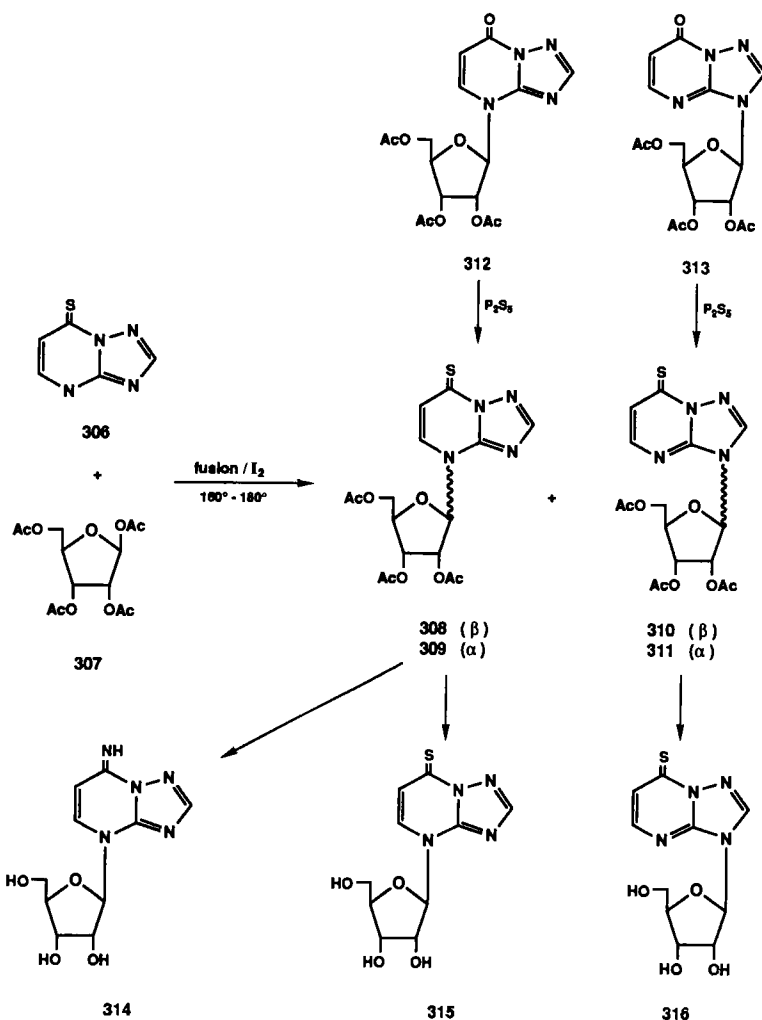
Rearrangement of 3-(per-*O*-acetylhexo or pentopyranosyl)-1,2,4-tria-





SCHEME 58

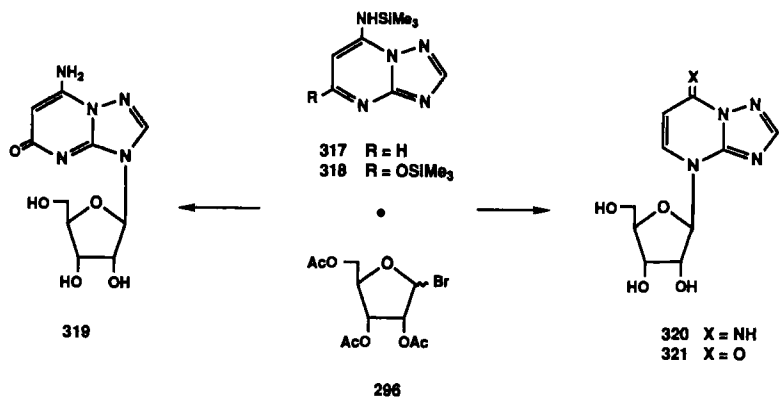
zolo[4,3-*a*]pyrimidines (**326**) with 1,8-diazabicyclo[4.5.0]undec-7-ene (DBU) in aprotic solvents gave the corresponding acetylated 2-glycosyl-1,2,4-triazolo[1,5-*a*]pyrimidines **327** (94MI1) (Scheme 62).



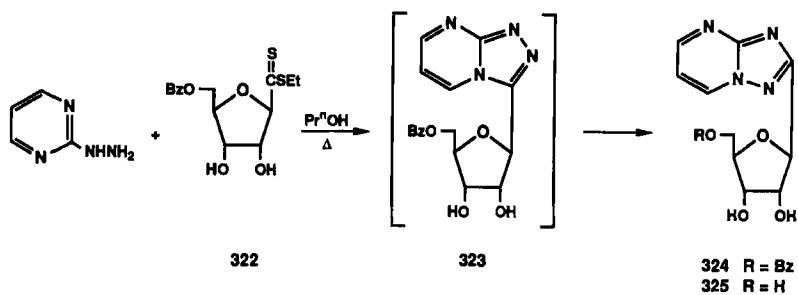
SCHEME 59

### 9. Uses and Biological Properties

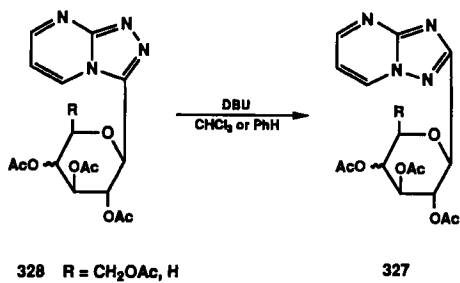
1,2,4-Triazolo[1,5-*a*]pyrimidinesulfonamides are used as herbicides, and plant growth inhibitors (92USP5163995; 93MIP1, 93USP5201938), and they show activity against acetolactate synthase (92MI3). Dual-inhibition analyses of the triazolopyrimidine sulfonanilide feedback inhibitor leucine reveal that the three herbicides were competitive with the amino acid for binding to acetolactate synthase from wild-type cotton cultures. Acetolac-



SCHEME 60



SCHEME 61



SCHEME 62

tate synthase-inhibiting herbicides may bind to the regulatory site on the enzyme (91MI3).

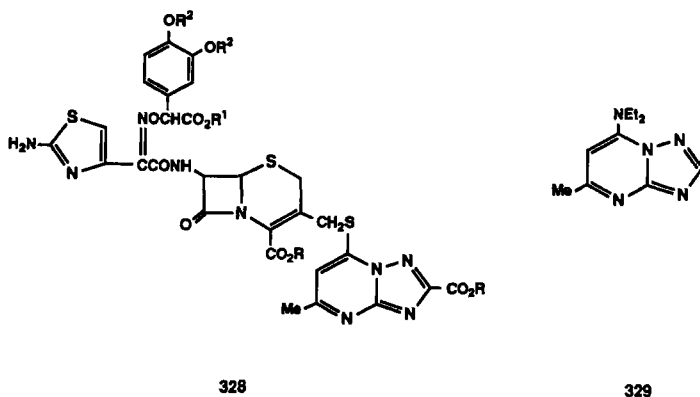
Compound **46** acts as a selective herbicide against dicotyledonous weeds, such as *Galium*, *Matricaria*, *Galinsoga*, and *Mercurialis* spp. in beets. The herbicidal activities of **46** vary according to the position of the substituent on the phenyl ring. The *ortho* position produces the highest levels of herbicidal activity against *Abutilon theophrasti* (90MI2). The 2-(Arylthio)-1,2,4-triazolo[1,5-*a*]pyrimidines **213** and **93** are also useful as herbicides (89EUP332029, 89EUP337232).

Compounds **97** and 5,7-dihalo-1,2,4-triazolo[1,5-*a*]pyrimidines act as agrochemical fungicides and cause protection against *Plasmopara viticola* (87GEP3533050; 94MIP1). Compounds **121** are superior fungicides (83GEP3130633).

Compounds **272** are useful as herbicides and inhibitors of nitrification of amino nitrogen in soil, and they are used for the control of *Echinochloa crusgalli* without damage to rice. 5-Fluoromethyl-7-methoxy-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamides are useful for the control of pigweed (85USP4818273).

5-Piperidino-7-[*N-n*-pentyl-*N*-( $\beta$ -hydroxyethyl)amino]-1,2,4-triazolo[1,5-*a*]pyrimidine has been complexed with  $\beta$ -cyclodextrin in 60% ethanol at 60°C to increase its solubility. The dissolution rate of the drug increased with increasing  $\beta$ -cyclodextrin content (91PHA225). (Triazolopyrimidinyl-methyl)biphenyls, which are angiotensin II receptor antagonists, are useful in the treatment of hypertension (93USP5231094; 94USP5358950). Some derivatives show antianginal, coronary blood flow-increasing, antiinflammatory, antifungicidal, gastric motility and secretion inhibitory, narcosis-potentiating, and spasmolytic activities (92EUP500136, 92EUP500137; 93EUP550113). Triazolopyrimidines having benzotriazolyl and phenylsulfonfyl groups are pharmacophores (95H729). 7-Amino-6-aminoalkyl-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidines are useful as bioactive compounds and intermediates (88EGP256327, 88EGP256328). The triazolopyrimidine **328** having fused  $\beta$ -lactam and 1,3-thiadiazolyl rings and **291** are useful as antibiotics (88EUP254495, 88EUP292230; 90EUP349296; 93EUP544166). Trapidil (**329**) is known as a useful antianginal drug, so the skeleton is of both chemical and medicinal interest. It was prepared by chlorodehydroxylation of **152** with POCl<sub>3</sub>, followed by amination with Et<sub>2</sub>NH (92MI4), and was purified by treatment with aqueous Cu(NO<sub>3</sub>)<sub>2</sub> · H<sub>2</sub>O in xylene [84JAP(K)59/29689] and used as an effective coronary vasodilator (Scheme 63).

Compounds **5** are used as neoplasm inhibitors (89EGP270711) and **14** as vasodilators, anticholesteremics, and blood platelet aggregation inhibitors [81JAP(K)81/127383]. Significant activity against histamine-induced bron-



SCHEME 63

chospasm vasodilators and use as a potent cardiotonic drug have been reported for **37** (82JMC420; 86EUP150974; 89USP4822404). Compounds **92** cause an increase in cardiac contractility (85USP4497814), and various 6-alkyl derivatives of this ring serve in the treatment and prevention of cardiovascular diseases, particularly hypertension and cardiac insufficiency, and diseases of the arterial wall, especially atherosclerosis (86JAP(K)61/227584; 87EGP246999; 89ZC378; 95USP5387747). 5-Butyl-4-(2'-triazolylbiphenylmethyl)-1,2,4-triazolo[1,5-*a*]pyrimidin-7-one is useful for the treatment of circulatory diseases such as hypertension, heart diseases, stroke, and arteriosclerosis [95JAP(K)07/157485]. Compound **197** is an effective vasodilator and a hypotensive and platelet aggregation inhibitor; it also has cholesterol-lowering activities. The derivative **193** inhibits aortic smooth muscle proliferation and is useful for the treatment of atherosclerosis [80JAP(K)80/51089; 82JAP82/35592; 83MIP1; 91JAP(K)03/118383]. The 5,7-diamino-1,2,4-triazolo[1,5-*a*]pyrimidines (**186**) are useful as antihypertensives, calcium blockers, platelet aggregation inhibitors, phosphodiesterase inhibitors and thromboxane A<sub>2</sub> inhibitors (86BEP903828).

Compounds **179** are useful as antiulcer agents and have coronary vasodilator, antidiabetic, and antiallergic activities. The amine derivatives **186** have antineoplastic activity. Thus, effects are found for **186** (NR<sup>1</sup>R<sup>2</sup> = NHBn; NR<sup>3</sup>R<sup>4</sup> = NHNH<sub>2</sub>) against AK755, **186** (NR<sup>1</sup>R<sup>2</sup> = NHBn; NR<sup>3</sup>R<sup>4</sup> = morpholino) against sarcoma 37, and **186** (NR<sup>1</sup>R<sup>2</sup> = NR<sup>3</sup>R<sup>4</sup> = phthalimidoethylthio) against Lewis Lung Cancer (81KFZ31). Triazolopyrimidine **187** is an antileukemic agent in mice.

The 7-pyrrolyl(indolyl)triazolopyrimidinium salts show antiviral activity against herpes simplex 1 and ospoviruses, and against classical avian plaque (90KFZ41). Compound **276** was prepared as a bolting inhibitor for sugar

beets (89USP4866063). 2-(2-Furyl)-1,2,4-triazolo[1,5-*a*]pyrimidine was prepared as a possible inhibitor of antioxidant enzymes [95IJC(B)209], and 7-phenoxyalkyl-1,2,4-triazolo[1,5-*a*]pyrimidines were prepared for possible treatment of seizures and neurological disorders (95MIP1).

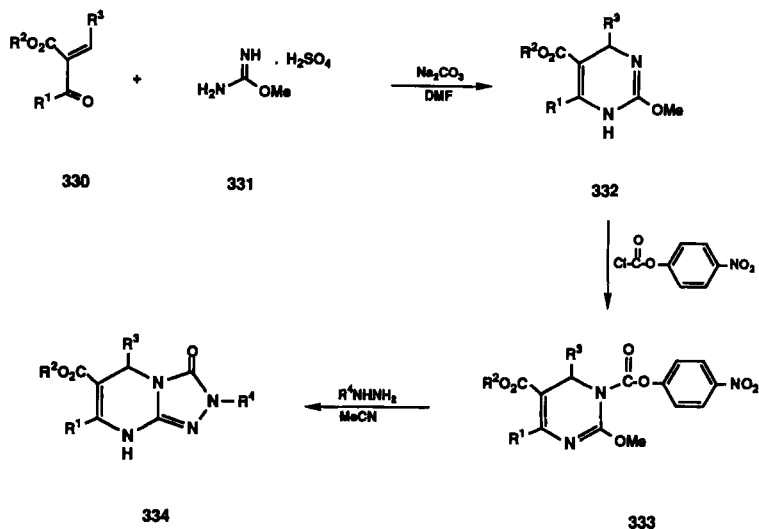
1,2,4-Triazolo[1,5-*a*]pyrimidines are used as development-inhibitor-releasing compounds in the processing of silver halide photographic material [91JAP(K)03/288148] to improve coating stability and sensitivity [87JAP(K)62/192736; 93JAP(K)05/19409; 93JAP(K)05/127279, 93JAP(K)05/232618]. Silver halide photographic materials containing 5- or 7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives provide high contrast, which is suitable for graphic arts use [88EUP292986; 90JAP(K)02/71254], and show good shelf life under conditions of high temperature and high humidity [89JAP(K)01/235957; 91JAP(K)03/10245]. Polymers containing the 1,2,4-triazolo[1,5-*a*]pyrimidinyl group are described for use as stabilizers in photographic silver halide materials (83GEP3223316). Compounds **95** were prepared as a photosensitive photographic element; they also act as a plant growth regulator and are useful as a tobacco-suckering agent (90EGP276620).

## B. 1,2,4-TRIAZOLO[4,3-*a*]PYRIMIDINES

### 1. *Synthesis from Pyrimidines*

The synthesis of this ring system may be achieved by building the triazole onto a preformed pyrimidine ring. Cyclocondensation of ketoesters **330** with *O*-methylisourea (**331**) gave the pyrimidine **332**, whose acylation gave the *N*-acyl derivative **333**, which can be cyclized with hydrazines to give **334** (89GEP3839711) (Scheme 64).

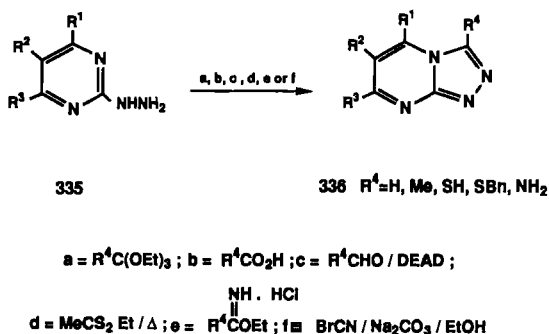
Cyclization of a 2-hydrazinopyrimidine with one-carbon-inserting reagents serves as a general route to this ring. Thus, cyclization of 2-hydrazinopyrimidines (**335**) with formic acid (57JCS727), orthoesters (60JCS1829; 77AJC2515; 80USP4209621), carbon disulfide in boiling pyridine (60JCS1829), carbon disulfide in acetonitrile at room temperature (75JHC1187), ethyl dithioacetate (83GEP3308203), or cyanogen bromide (66CB2237; 80UKZ835) afforded the triazolo[4,3-*a*]pyrimidines (**336**). Reaction of **335** with aldehydes followed by cyclization with diethyl azodicarboxylate (DEAD) (77AJC2515) or with LTA in benzene gave **336** (57JCS727). Cyclization of 2-hydrazinopyrimidines (**335**) with ethyl imidate hydrochlorides afforded the 3-substituted 1,2,4-triazolo[4,3-*a*]pyrimidines **336**. However, when the 2-hydrazinopyrimidine (**335**,  $R^1 = R^2 = R^3 = H$ ) and 4,6-dimethyl-2-hydrazinopyrimidine (**335**,  $R^1 = R^3 = Me$ ,  $R^2 = H$ )



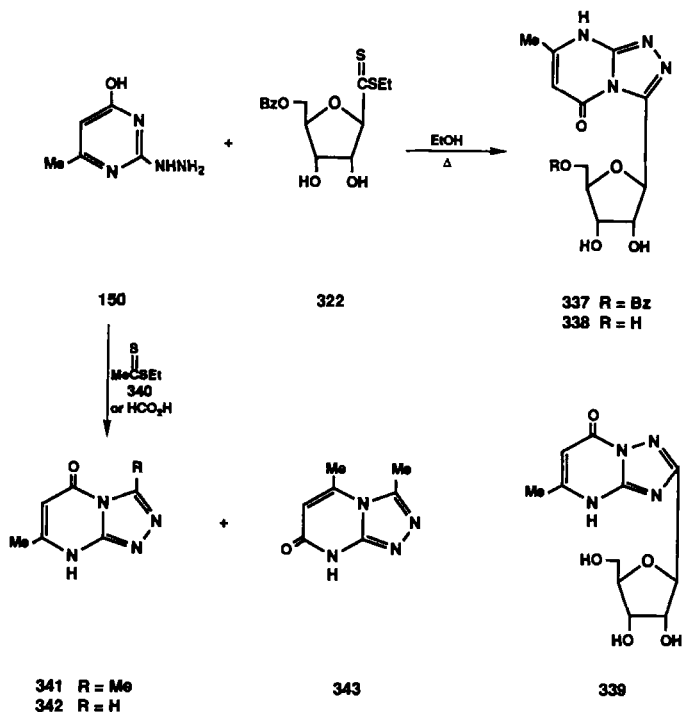
SCHEME 64

were cyclized with the imidate hydrochlorides, the isomeric triazolo[1,5-*a*]pyrimidines were formed [67JCS(C)498] (Scheme 65).

Coupling 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**322**) with 2-hydrazino-4-hydroxy-6-methylpyrimidine (**150**) afforded the blocked nucleoside **337**, which upon debenzoylation with methanolic ammonia gave 7-methyl-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrimidine (**338**). No rearranged product, such as **339**, was isolated (89MI3). Reaction of **150** with ethyl dithioacetate (**340**) gave a mixture of 3,7(3,5)-dimethyltriazolo[4,3-*a*]pyrimidinones **341** and **343** (89H239), whereas the reaction with formic acid gave **342** (78MIP1) (Scheme 66).

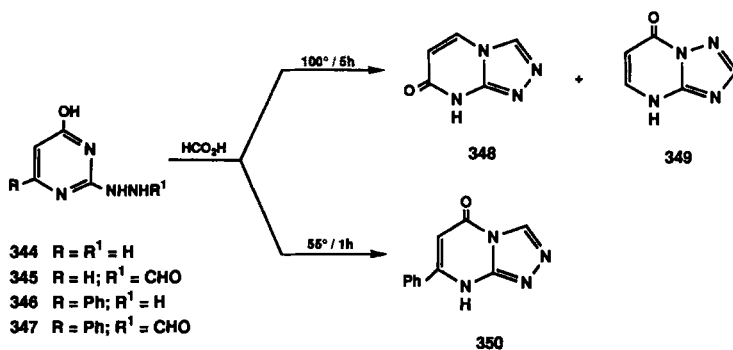


SCHEME 65



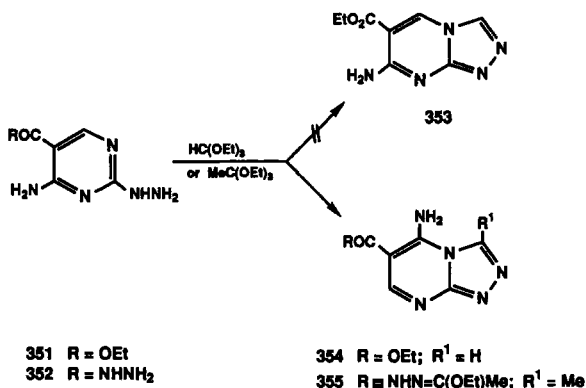
SCHEME 66

Boiling the hydrazinopyrimidinone **344** in formic acid or thermolysis of **345** in *o*-xylene gave the isomeric triazolopyrimidinones **348** and **349**, but heating **346** with formic acid afforded the dihydrotriazolo[4,3-*a*]pyrimidin-5-one **350** and the formylhydrazinopyrimidine derivative **347**, whose heating in formic acid gave **350** (70CB3266; 71CB2702) (Scheme 67).



SCHEME 67





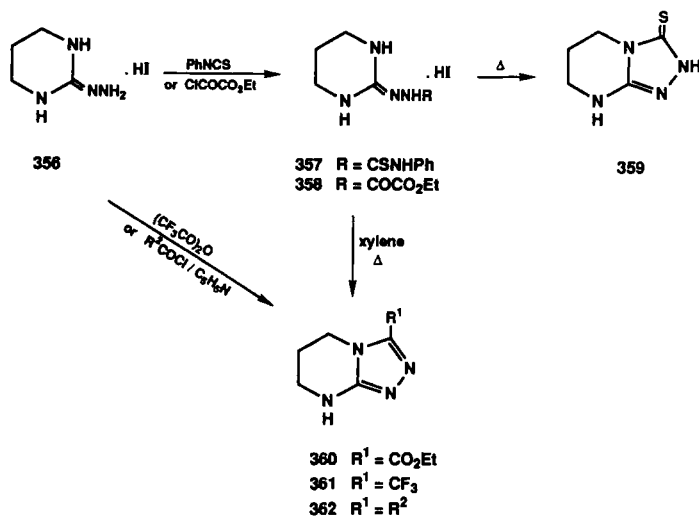
SCHEME 68

Condensation of 4-amino-5-ethoxycarbonyl-2-hydrazinopyrimidine (**351**) with triethyl orthoformate gave 5-amino-6-ethoxycarbonyl-1,2,4-triazolo[4,3-*a*]pyrimidine (**354**) and not the isomeric 6,7-disubstituted derivative **353**. Similarly, **352** and triethyl orthoacetate gave 5-amino-6-(2-ethoxy)ethylidenecarbazoyl-3-methyl-1,2,4-triazolo [4,3-*a*]pyrimidine (**355**) (86H1899) (Scheme 68).

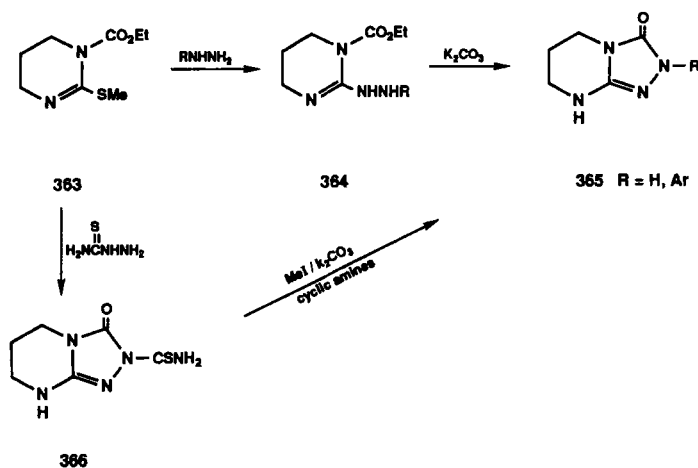
Reaction of 2-hydrazonohexahydropyrimidine hydroiodide (**356**) with phenyl isothiocyanate gave the semicarbazone **357**, which upon heating gave 3-thioxotetrahydrotriazolopyrimidine (**359**) whereby aniline was eliminated. Acylation of **356** with ethyl oxalyl chloride gave **358**, which cyclized in xylene to the 3-ethoxycarbonyl derivative **360** and not to the pyrimido-1,2,4-triazine. Boiling **356** with trifluoroacetic anhydride or acyl chloride in dry pyridine gave **361** and **362**, respectively (94PHA27) (Scheme 69).

Triazolopyrimidinones (**365**) were prepared by the displacement of the *S*Me group from the pyrimidine derivative **363** with hydrazine or arylhydrazines to give the pyrimidinylhydrazines (**364**), which subsequently cyclized with  $\text{K}_2\text{CO}_3$  (86H93, 86JPR331). Reaction of **363** with thiosemicarbazide gave **365** ( $R = \text{H}$ ) via 2-aminothiocarbonylhexahydrotriazolopyrimidinone (**366**) as a result of splitting of the N-2-CS bond. Successive action of MeI, aqueous  $\text{K}_2\text{CO}_3$ , and cyclic amines converted **366** to **365** ( $R = \text{H}$ ) (87KGS1540) (Scheme 70).

The 4-aminopyrimidines **367** and **368** were prepared by the reaction of the benzylidene malononitriles with thiourea or *S*-methylisothiourea, respectively. Nucleophilic substitution at the 2-position of **368** with hydrazine gave the 2-hydrazino derivative **369**, whose treatment with carbon disulfide yielded the triazolopyrimidine **373** rather than its isomeric compound [83ZN(B)1686]. Heating **369** with benzoyl chloride in anhydrous dioxane,

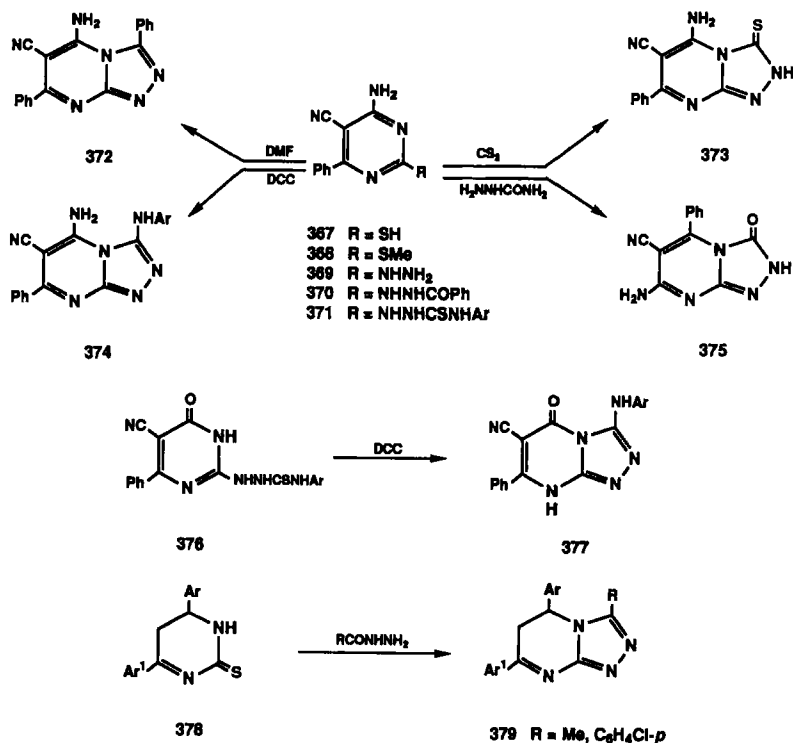


SCHEME 69



SCHEME 70

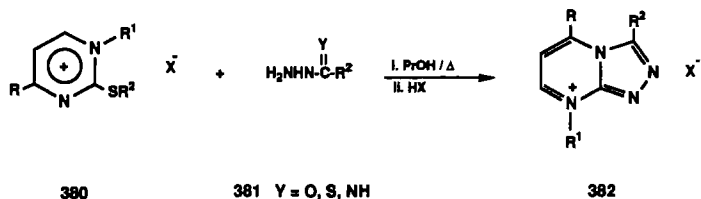
afforded the *N*-benzoyl derivative **370**, whose ring closure took place upon heating in DMF to give 5-amino-6-cyano-3,7-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidine (**372**). The latter can also be obtained by direct reaction of **368** with benzoylhydrazine in DMF (87JHC1605). The isomeric 1,2,4-triazolo-[4,3-*a*]pyrimidin-3-one **375** was obtained from **368** by reaction with semicarbazide (88SUL203). Reaction of **369** with isocyanates gave thiosemicabazides (**371**), whose cyclodesulfurization with DCC gave **374** (95MI1).



SCHEME 71

Similarly, cyclodesulfurization of **376** gave **377**. Cyclization of the dihydropyrimidinethione **378** with acetylhydrazine or *p*-chlorobenzoylhydrazine gave the triazolopyrimidine **379** (91MI2; 93RRC701) (Scheme 71).

The 8-substituted 1,2,4-triazolo[4,3-*a*]pyrimidinium salts (**382**) were prepared from pyrimidinium salts (**380**) with hydrazines (**381**) in boiling propanol followed by treating the mixture with acid (81EGP147944) (Scheme 72).

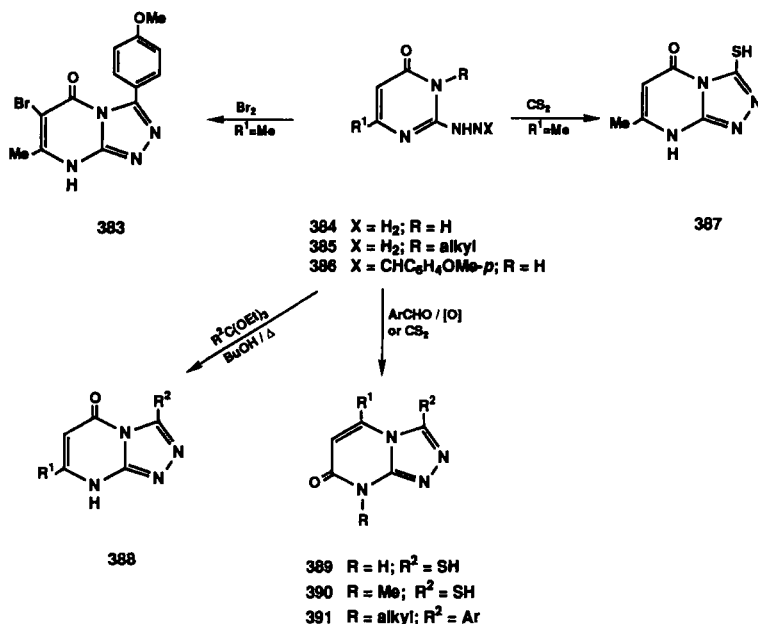


SCHEME 72

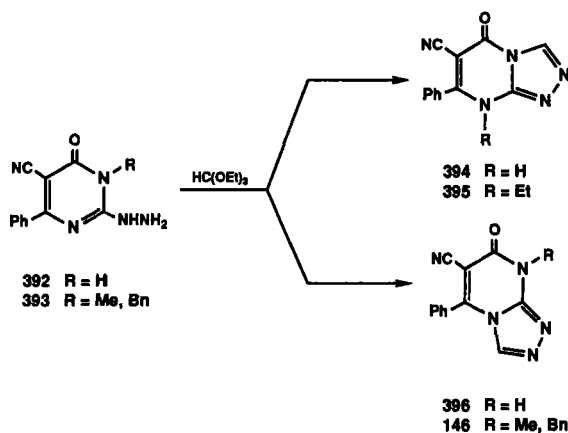
Condensation of 2-hydrazinopyrimidine (**384**) with an aromatic aldehyde formed the Schiff bases (**386**), which then cyclized with bromine to 6-bromo-1,2,4-triazolo[4,3-*a*]pyrimidine (**383**) and with carbon disulfide to **387** (92PS145). A similar cyclization was effected also on **384** to give **388** (68T2839; 85FRP2549834), but the cyclization of **384** or **385** with carbon disulfide afforded 3-thiolo-1,2,4-triazolo[4,3-*a*]pyrimidin-7-ones **389** and **390**, respectively. A small amount of the isomeric 3-thiolo-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one was isolated in the former case (68T2839). Reaction of **385** with benzaldehyde [67JCS(C)498] or *p*-chlorobenzaldehyde (90MI3) followed by oxidation with LTA in benzene afforded **391** (Scheme 73).

Cyclization of 2-hydrazinocyanopyrimidinone **392** with triethyl orthoformate afforded the triazolopyrimidin-5-one **394** rather than **396**, together with its *N*-ethylated derivative **395**, whose amount increased with time. Here the orthoester acts as a novel alkylating agent. The products from reaction with *N*-substituted pyrimidinones (**393**) were the triazolopyrimidin-7-ones **146** (98UP1) (Scheme 74).

3-Amino-2-hydrazino-4(3*H*)-pyrimidinone (**397**) and orthoesters in hot acetic acid or BuOH gave 1,2,4-triazolo[4,3-*a*]pyrimidin-7(8*H*)-ones **398**. When the heating in acetic acid was continued overnight, the acetamido derivative **399** was obtained. In acetic acid at room temperature, the re-



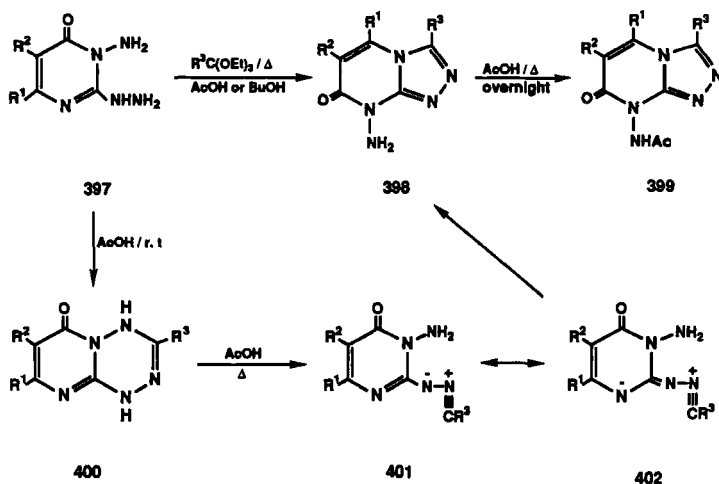
SCHEME 73



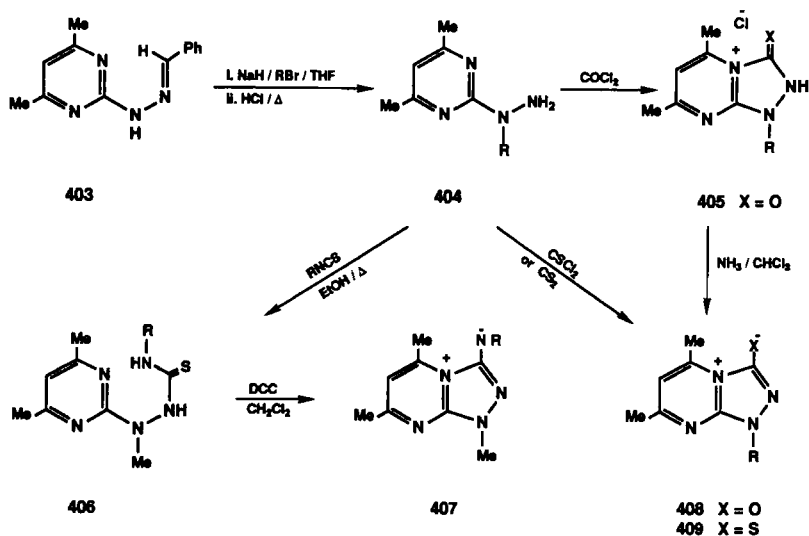
SCHEME 74

action of **397** with orthoesters, dimethylformamide dimethylacetal, or diethoxymethylacetate gave a mixture of **398** and 6*H*-pyrimido[1,2-*b*]-1,2,4,5-tetrazin-6-ones (**400**) (87JOC2220). The latter underwent a thermal acid-catalyzed rearrangement to **398**. The mechanism may be rationalized by the initial protonation at the N-4 of **400** followed by generation of the nitrile imine **401**, a dipolar species (**402**) that readily electrocyclicized to **398** (Scheme 75).

The 1*H*-1,2,4-triazolo[4,3-*a*]pyrimidinium betaine was prepared by the alkylation of hydrazone (**403**) followed by hydrolysis to hydrazine (**404**)



SCHEME 75



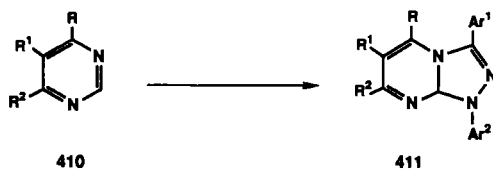
SCHEME 76

and treatment with phosgene to give **405**. The latter with ammonia gas gave 1*H*-1,2,4-triazolo[4,3-*a*]pyrimidinium-3-olates **408** [88JCS(P1)351]. The 3-thiolate analogs **409** were formed by treating **404** with thiophosgene or carbon disulfide. The hydrazinopyrimidine **404** was converted into the 1,2,4-triazolo[4,3-*a*]pyrimidinium-3-aminide **407** with isothiocyanate to give the hydrazinopyrimidine **406**, which then was cyclized by DCC [88JCS(CC)506; 93JCS(P1)705] (Scheme 76).

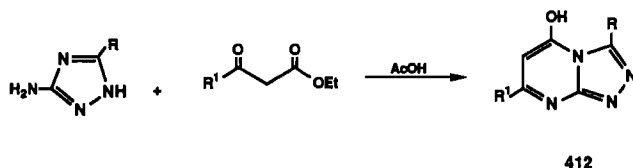
1,3-Dipolar cycloaddition of a 1,3-diarylnitrilimine with pyrimidine (**410**) gave the stable monoadduct 1,8*a*-dihydro-1,2,4-triazolo[4,3-*a*]pyrimidine (**411**) (94LA1005) (Scheme 77).

## 2. Synthesis from Triazoles

Triazolopyrimidine rings may also be formed by constructing the pyrimidine ring onto a preformed triazole. Reaction of ethyl acetoacetate with 3-amino-5-substituted-1,2,4-triazoles in glacial acetic acid led to the for-



SCHEME 77



SCHEME 78

mation of 1,2,4-triazolo[4,3-*a*]pyrimidine (**412**), involving the amino group and the N-4 of the triazole ring (57JCS727); the product from the reaction with ethyl benzoylacetate has been given the oxo form of **412** (70CB3266; 71CB2702) (Scheme 78).

3-Amino-1,2,4-triazole with methyl propiolate (**413a**) gave the two isomeric triazolopyrimidinones **348** and **414**, but with methyl phenylpropiolate (**413b**) gave **348a** only (70CB3266; 71CB2702). The use of dimethyl acetylenedicarboxylate yielded the two isomers of oxodihydrotriazolopyrimidines **415** and **416**, and a small amount of the 1:1 adduct **417** (Schemes 79 and 80).

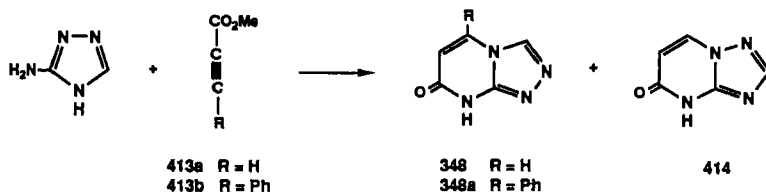
Condensation of 3-amino-1,2,4-triazole with the chalcone **418** and 1-(3-dimethylaminopropionyl)naphthalene (**419**) gave the triazolopyrimidines **420** and **421**, respectively (89PHA820) (Scheme 81).

Reaction of Schiff bases **422** with a mixture of phosphorus oxychloride and dichloroacetic acid in DMF gave triazolopyrimidinones (**423**) instead of the expected 3,3-dichloroazetidinones (**424**) (88JHC173). 1,4-Cycloaddition of **422** ( $R = \text{SMe}$ ;  $R^1 = \text{Ph}$ ) with phenoxyacetyl chloride in the presence of triethylamine gave the dihydro-1,2,4-triazolo[4,3-*a*]pyrimidinone **425** (88JHC173) (Scheme 82).

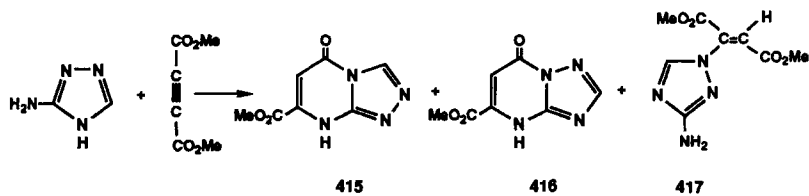
### 3. Reactivity

A major type of reactivity of this ring is concerned with its rearrangement to heterocycles having the [1,5-*a*] ring junction. Consequently, it is discussed either in this section or under the synthesis of the [1,5-*a*] type.

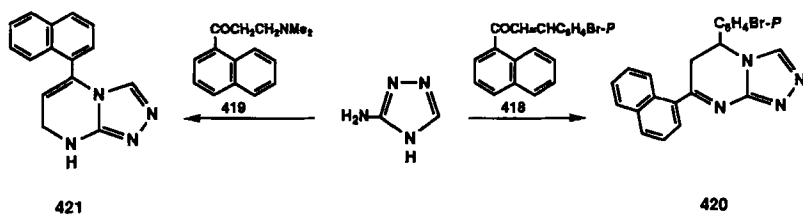
Benylation of **336** ( $R^4 = \text{SH}$ ) gave the corresponding 3-benzylthio de-



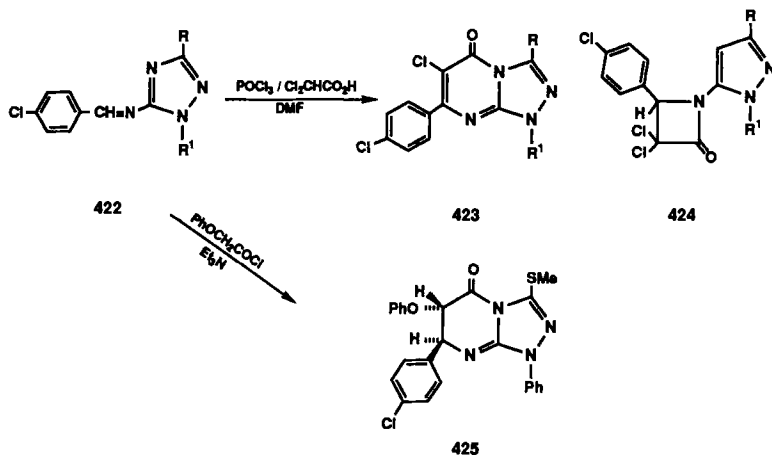
SCHEME 79



SCHEME 80



SCHEME 81



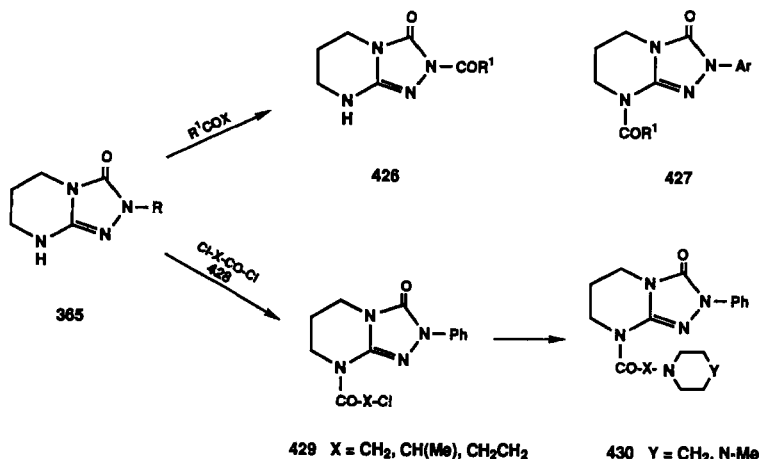
SCHEME 82



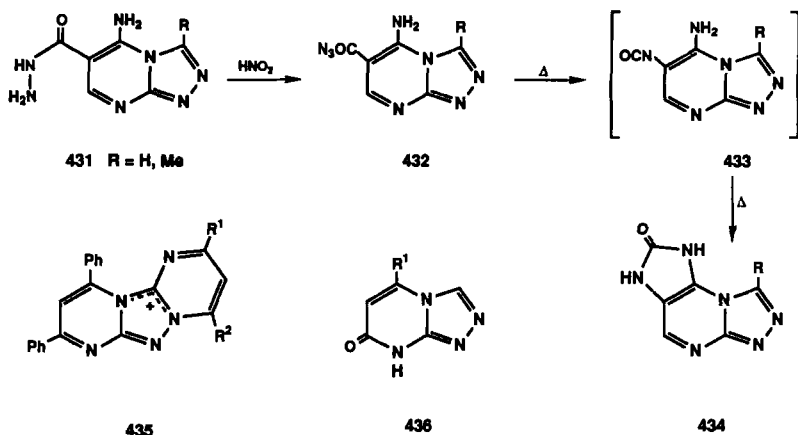
rivative (75JHC1187). Alkylation of **394** with MeI/K<sub>2</sub>CO<sub>3</sub> or BnCl/NaOH gave the 8-alkylated derivatives (98UP1). Acylation of 3-oxohexahydrotriazolopyrimidine (**365**; R = H) with acid chlorides, acid anhydrides, alkyl chloroformates, and alkyl and aryl isocyanates gave the 2-acyl derivatives **426** (86H93, 86JPR331), whereas acylation of **365** (R = Ar) gave **427** (86KGS1350). Chloroacylation of **365** (R = Ph) with **428** led to **429**, whose amination with piperidine or *N*-methylpiperazine afforded 8-aminoacyl-2-phenyl-3-oxo-2,3,5,6,7,8-hexahydro-1,2,4-triazolo[4,3-*a*]pyrimidines (**430**) (88PHA723). The ester **416** can be converted to its corresponding acid, sodium salt, and piperidino derivative (71CB2702) (Scheme 83).

Nitrosation of **431** with nitrous acid afforded 5-amino-6-azidocarbonyl-1,2,4-triazolopyrimidine (**432**), which was thermally transformed through Curtius rearrangement into 1,2,4-triazolo[3,4-*b*]purin-7(8*H*)-ones (**434**) via the isocyanate intermediate **433** (86H1899). Treatment of 3-amino-5,7-diphenyl-1,2,4-triazolo[4,3-*a*]pyrimidine with 1,3-dicarbonyl compounds yielded 1,2,4-triazolo[1,5-*a*:4,3-*a'*]dipyrimidinium salts (**435**) (66CB2237; 80UKZ835). Desulfurization of 3-thiolo-1,2,4-triazolo[4,3-*a*]pyrimidinones (**389**) with a solution of nitric acid and sodium nitrite gave **436** (68T2839) (Scheme 84).

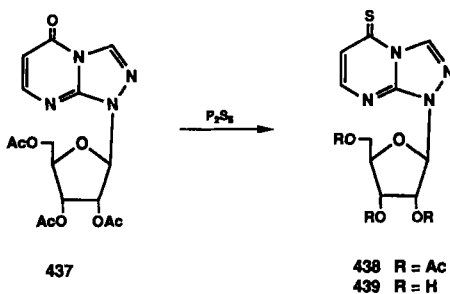
Thionation of 1-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazolo[4,3-*a*]pyrimidin-5-one (**437**) with phosphorus pentasulfide afforded the 5-thione **438**, whose deacetylation with methanolic ammonia gave **439** (78MI1) (Scheme 85).



SCHEME 83



SCHEME 84



SCHEME 85

#### 4. Physicochemical Data

The crystal structures of 3-(4-pyridinyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrimidine and its 6-hydroxy derivative have been solved by direct methods and refined by anisotropic full-matrix least-squares and found to be in the triclinic and monoclinic space groups, respectively. In the solid state both molecules have the same conformation and are packed similarly. The planarity of the condensed triazole ring and its  $\pi$ -electrons conjugated with a lone pair at N-8 of the saturated diazine rings were reported (94MI3). The molecular structure of **408** was determined by X-ray crystallography [88JCS(CC)506; 93JCS(P1)705].

$^1\text{H}$  NMR spectroscopy was used to deduce the *trans* configuration of the dihydrotriazolopyrimidinone substituents from the  $J_{\text{H,H}}$  coupling constants (11 ppm) of the respective protons (88JHC173). 2D NMR spectroscopy was used to identify the two isomers **341** and **343** (89H239).

## 5. Uses and Biological Properties

Silver halide emulsion layers containing the substituted 5(7)-hydroxytriazolo[4,3-*a*]pyrimidine derivatives are used as photographic materials [91JAP(K)03/13934].

3-Oxo-1,2,4-triazolo[4,3-*a*]pyrimidine-6-carboxylates **334** were prepared as calcium-channel-blocking vasodilators useful as antihypertensives (89GEP3839711). Compound **388** and 6-*aralkyl* derivatives showed cardiovascular activity (85FRP2549834; 95USP5387747). Triazolo[4,3-*a*]pyrimidines with an aryl substituent on the pyrimidine ring were reported to be useful as anxiolytic agents (80USP4209621).

### C. 1,2,4-TRIAZOLO[1,5-*c*]PYRIMIDINES

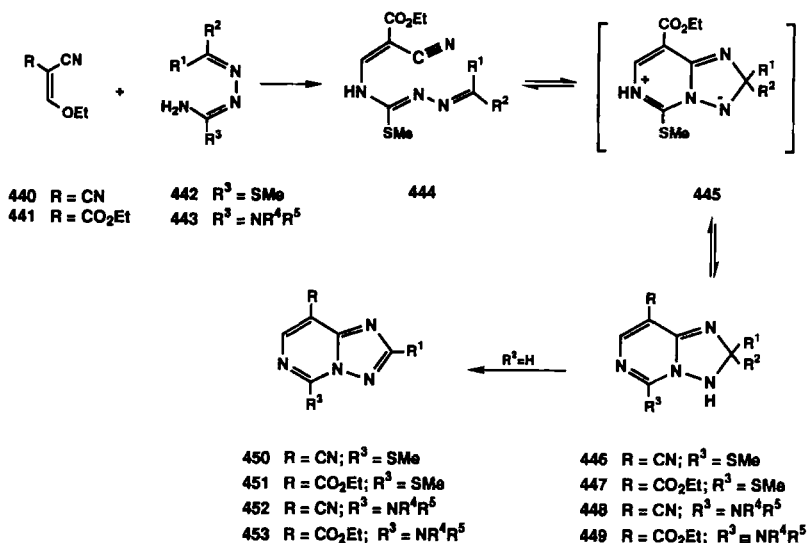
#### 1. Open Chain Precursors for Synthesis

This ring can be prepared by the cyclization of 4-[2-cyano-2-(ethoxycarbonyl)vinyl]-3-methylisothiosemicarbazones of aromatic aldehydes (**444**;  $R^2 = H$ ), obtained from the reaction of **441** with **442** by heating in BuOH/DMF/dioxane or in pyridine to give triazolopyrimidines **451** in moderate yields. Competitive formation of ethyl 4-amino-2-(methylthio)pyrimidine-5-carboxylate takes place. Treatment of the respective aromatic ketones with hot acetic acid or pyridine gave 2,2,5-trisubstituted 2,3-dihydrotriazolopyrimidine-8-carboxylates (**447**) by intramolecular cycloaddition of **444** via the intermediate **445**. The ring closure of **444** may involve a 10-electron cyclic transition state (81JOC3956). Condensation of ethoxymethylenemalononitrile (**440**) with isothiosemicarbazones (**442**) gave the dihydrocyano analogs **446**, which were readily oxidized in DMSO to the triazolopyrimidines (**450**) (81BCJ1767). Similarly, condensation of diaminomethylenehydrazones (**443**) with **440** and **441** in the presence of MeCN/Et<sub>3</sub>N gave directly the 2,3-dihydro-1,2,4-triazolo[1,5-*c*]pyrimidines **448** and **449**, respectively. The reaction was initiated by the attack of the amino group of **443** on the ethoxymethine carbon of **440** or **441**, followed by an electrocyclic reaction. Compounds **448** and **449** were oxidized with FeCl<sub>3</sub>/AcOH or I<sub>2</sub>/EtOH to give the triazolopyrimidines **452** and **453**, respectively (85CPB2678; 88CPB1963) (Scheme 86).

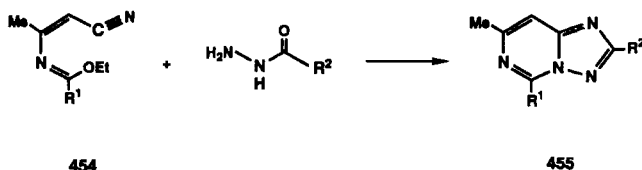
Condensation of the imidates **454** with hydrazides gave 1,2,4-triazolo[1,5-*c*]pyrimidines **455** (89MI1) (Scheme 87).

#### 2. Synthesis from Pyrimidines

Reaction of amine **456** with DMF/DMA, followed by hydroxylamine and then acetylation gave the acetoxymethylaminomethyleneaminopyrimidine



SCHEME 86

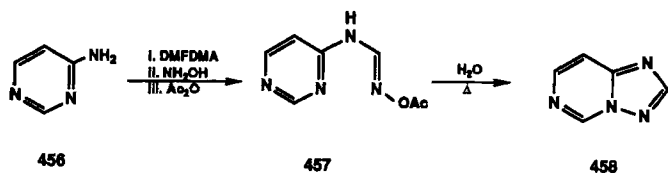


SCHEME 87

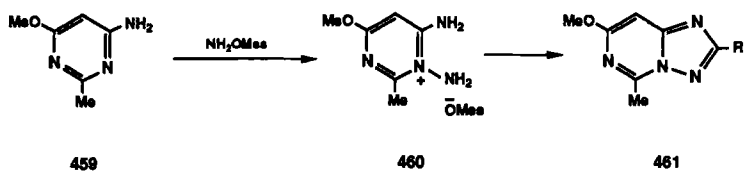
**457**, which subsequently cyclized to **458** by heating in water (76S833) (Scheme 88).

Amination of the 4-aminopyrimidine **459** with *O*-mesitylenesulfonylhydroxylamine gave the *N*-aminopyrimidinium salt **460**, which was transformed into 1,2,4-triazolo[1,5-*c*]pyrimidines (**461**) by heating with formic acid, acetic anhydride, or benzoyl chloride (75JHC107). Similarly, the reactions of 1,6-diaminopyrimidine **462** with benzoyl chloride (92MI1), triamine **464** with formic acid (79KGS262), and aminoiminopyrimidine **466** with orthoesters (92MI2) gave the triazolo[1,5-*c*]pyrimidines **463**, **465**, and **467**, respectively (Schemes 89–91).

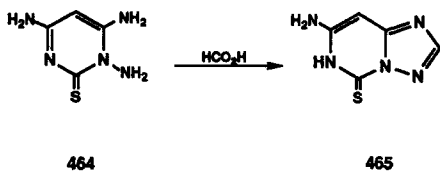
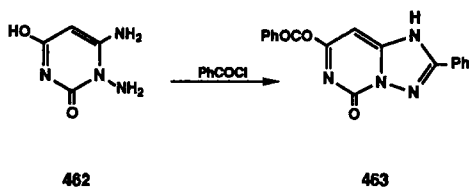
Formation of 1,2,4-triazolo[1,5-*c*]pyrimidine-5(6*H*)-thiones or their 5(6*H*)-ones by the reaction of 1,4,6-triaminopyrimidine-2(1*H*)-thiones (**468**) with the Vilsmeier reagent has been found to be dependent on the temperature. Thus, treatment of **468** with phosphoryl chloride and DMF at 0–5°C afforded mainly the thiadiazolopyrimidinium chloride **470** in addition to the thione **471**, but at 25°C a mixture of **471** and 7-formamido-1,2,



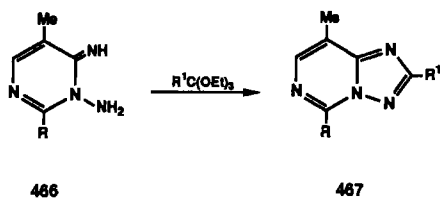
SCHEME 88



SCHEME 89



SCHEME 90



SCHEME 91

4-triazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**475**;  $R^1 = H$ ) was formed. Exclusive formation of **475** ( $R^1 = H$ ) was furnished at 70°C. The synthesis of 7-amino-2-methyl (**472**) and 2-phenyltriazolopyrimidine (**473**) was achieved by the reaction of **468** with phosphoryl chloride and *N,N*-dimethylacetamide or *N,N*-dimethylbenzamide, respectively; no thiadiazolopyrimidine derivatives were obtained. The 7-amino-2-substituted 1,2,4-triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones (**476**) were prepared by treatment of **472** and **473** with chloroacetic acid followed by acid hydrolysis or by the Vilsmeier-type reaction of **469** to furnish the amide **475** followed by acid hydrolysis (90JHC851). Compound **474** was prepared by the reaction of **468** with cyanogen bromide (90JHC851) (Scheme 92).

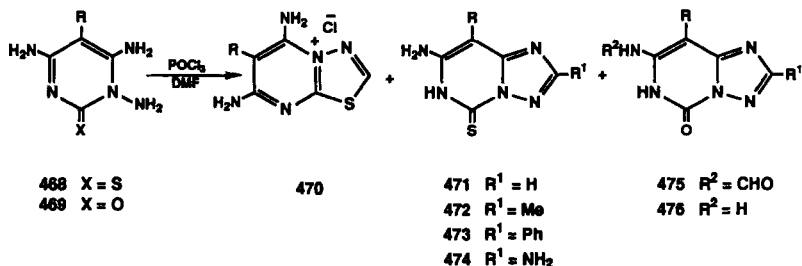
### 3. Synthesis from Triazoles

Reaction of 5-(2-aminoethyl)-1,2,4-triazole dihydrochloride (**477**) with aromatic aldehydes or ketones gave the azomethines **478** together with their cyclized tautomers **479**. Dithiocarbamate (**480**), obtained from **477** and  $CS_2/NaOH$ , cyclized with ethyl chloroformate to give the tetrahydrotriazolo[1,5-*c*]pyrimidine-5-thione **481**. Also the triazolopyrimidine derivatives **482** were prepared by reacting **477** with bis-methylthiolydenemalononitrile or bis-methylthiolydenecyanamide, respectively (92JPR630) (Scheme 93).

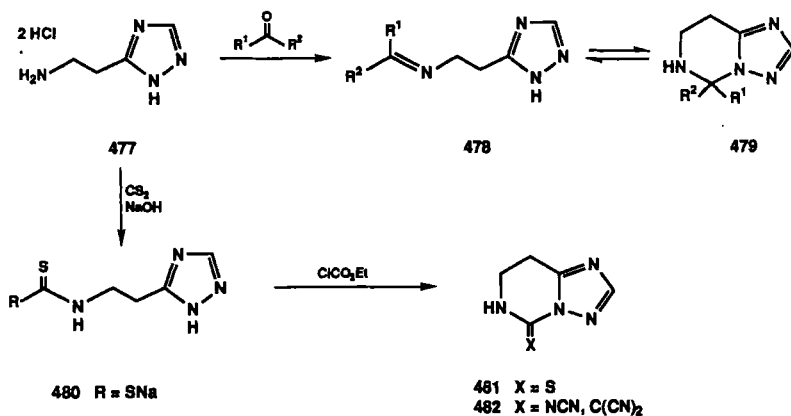
The nitrotriazolopyrimidine ring **484** can be constructed from 2-(3-aryl-1,2,4-triazol-5-yl)-2-nitro-1,1-ethenediamines (**483**) with triethyl orthoformate and trifluoroacetic acid (94JHC1171) (Scheme 94).

### 4. Dimroth Rearrangement of 1,2,4-Triazolo[4,3-*c*]pyrimidines

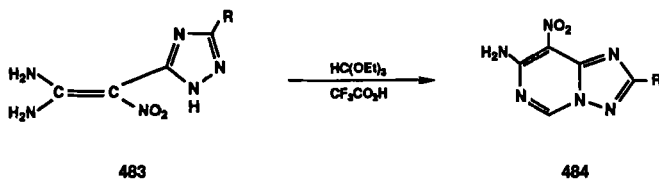
A characteristic feature observed during the cyclization of some hydrazino derivatives of pyrimidines is the rearrangement of the triazolo[4,3-*c*]pyrimidine intermediate to the triazolo[1,5-*c*]pyrimidine product.



SCHEME 92



SCHEME 93

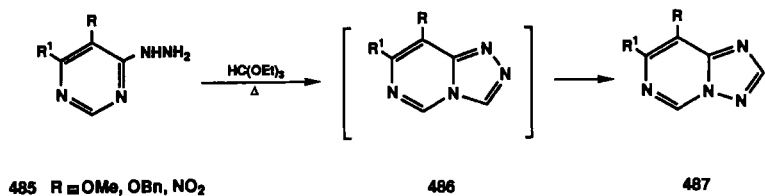


SCHEME 94

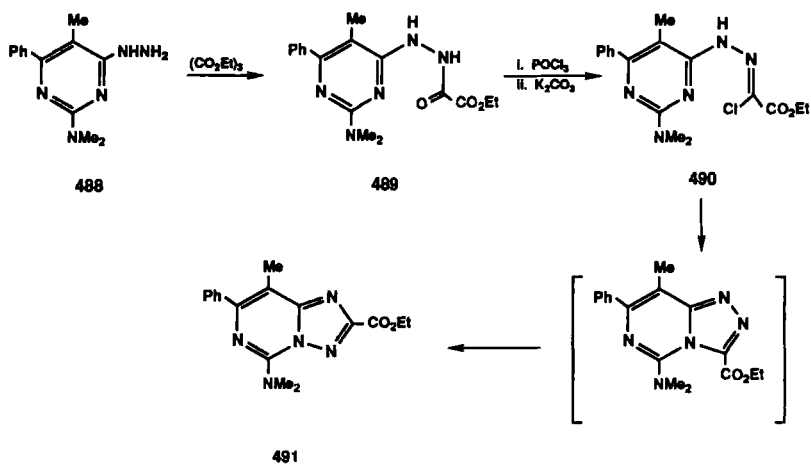
Cyclization of 5-methoxy(nitro)-4-hydrazinopyrimidines (**485**) with triethyl orthoformate gave the 1,2,4-triazolo[4,3-*c*]pyrimidine intermediate **486**, which cannot be isolated due to its conversion to its [1,5-*c*] isomer **487** by a Dimroth rearrangement. However, the 5-benzyloxy pyrimidine derivative, under the same conditions, afforded a mixture of the 8-benzyloxy derivatives of both [4,3-*c*] and [1,5-*c*] isomers **486** and **487**, respectively (86TL3127; 89JHC687; 90H277) (Scheme 95).

Heating hydrazinopyrimidine (**488**) in diethyl oxalate gave **489**, which upon chlorination with phosphorus oxychloride yielded (2-ethoxycarbonyl) triazolo[1,5-*c*]pyrimidine (**491**). The intermediate hydrazidoyl chloride **490** can be isolated under mild conditions (90T3897) (Scheme 96).

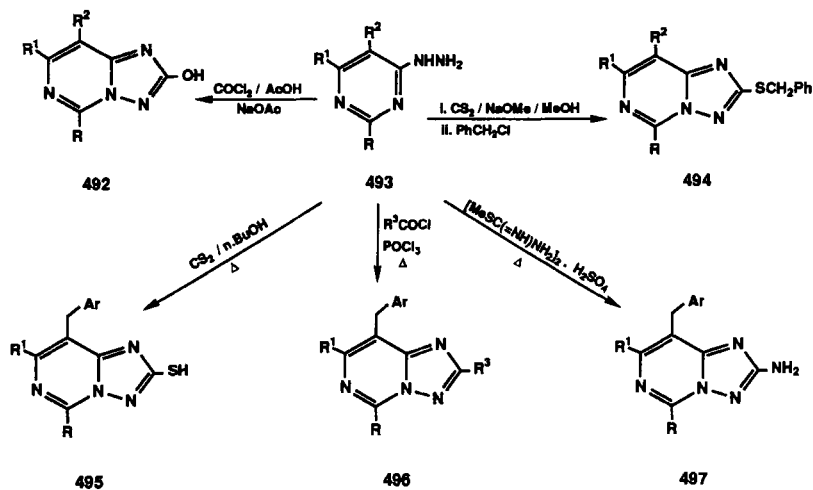
Substituted 1,2,4-triazolo[1,5-*c*]pyrimidines (**492**) were prepared from 4-hydrazinopyrimidine (**493**) and phosgene (85USP4528288). Reaction of **493** with carbon disulfide in sodium methoxide followed by boiling with benzyl chloride gave **494** (93USP5177206). A series of 2-substituted 1,2,4-triazolo[1,5-*c*]pyrimidines (**495–497**) were prepared from the hydrazine **493** ( $R^2 = CH_2Ar$ ) by heating it in carbon disulfide, acid chloride, and 2-methyl-2-thiopseudourea sulfate, respectively (94JMC2371) (Scheme 97).



SCHEME 95

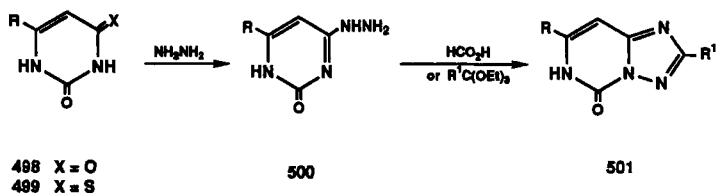


SCHEME 96



SCHEME 97



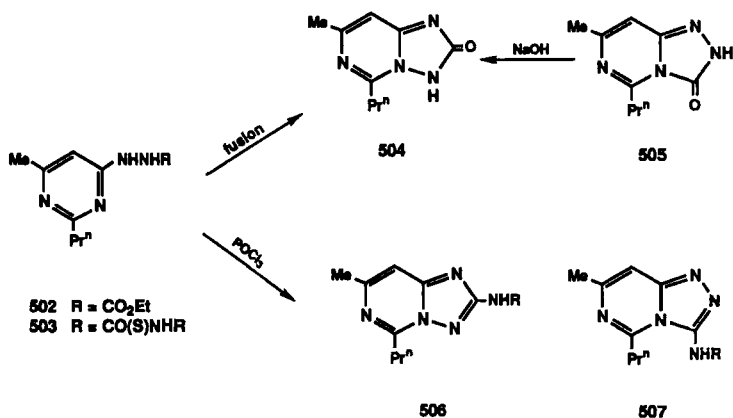


SCHEME 98

The triazolo[1,5-*c*]pyrimidinone **501** was prepared by converting uracil and its 6-methyl derivative **498** into the corresponding 4-thio derivatives (**499**) and thence into the hydrazinopyrimidinone **500**. This underwent cyclization in boiling formic acid, triethyl orthoacetate, or triethyl orthobenzoate to the triazolo[1,5-*c*]pyrimidinones **501** (80AJC1147) (Scheme 98).

Fusion of the ethoxycarbonyl derivative **502** afforded 2-oxotriazolo[1,5-*c*]pyrimidine (**504**), which was obtained alternatively by the isomerization of the corresponding [4,3-*c*] isomer **505** in NaOH solution. Treatment of the 4-semicarbazido- and 4-thiosemicarbazidopyrimidines (**503**) with POCl<sub>3</sub> gave the 2-aminotriazolo[1,5-*c*]pyrimidine **506** instead of the 3-amino isomer **507** (65JCS3357) (Scheme 99).

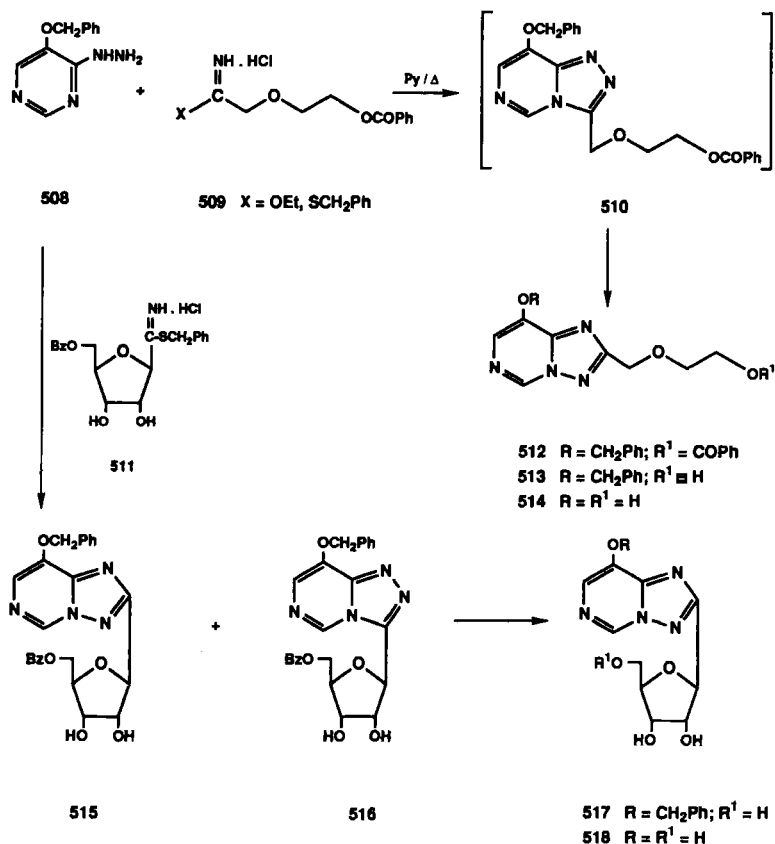
The acyclic *C*-nucleoside 2-(2-hydroxyethoxymethyl)-8-hydroxy-1,2,4-triazolo[1,5-*c*]pyrimidine (**514**) was obtained by condensation of 5-benzyloxy-4-hydrazinopyrimidine (**508**) with the imidates **509** in the presence of pyridine to give the triazolo[1,5-*c*]pyrimidine **512** via rearrangement of the [4,3-*c*]intermediate **510**. Cleavage of the ester group by ammonia in methanol gave **513**, which upon hydrogenolysis of the benzyl group afforded **514**. Condensation of **508** with thiobenzyl-5-benzoyloxy-β-D-ribofuranosyl-



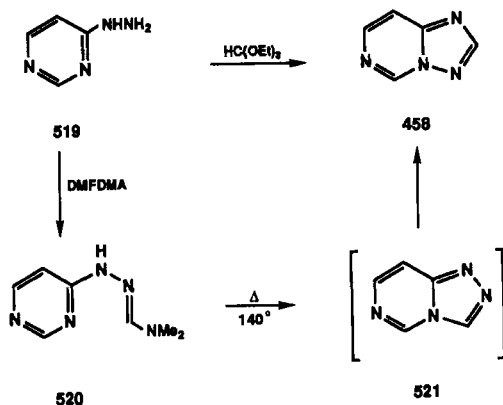
SCHEME 99

formimidate (**511**) afforded a mixture of the two *C*-nucleosides **515** and **516**. Action of methanolic ammonia on **515** or its isomer **516** gave **517**, which upon hydrogenolysis gave **518**. The rearrangement of 3-( $\beta$ -D-ribofuranosyl)triazolo[4,3-*c*]pyrimidine (**516**) to 2-( $\beta$ -D-ribofuranosyl)triazolo-[1,5-*c*]pyrimidine (**517**) took place during debenzoylation as a consequence of the alkaline conditions (89JHC991) (Scheme 100).

Although the reaction of hydrazinoazines and triethyl orthoformate usually gives the unrearranged products, the 4-hydrazinopyrimidine **519** afforded with the same reagent the rearranged product 1,2,4-triazolo[1,5-*c*]pyrimidine (**458**) (76S833). The same heterocycle (**458**) was obtained also from the reaction of **519** with DMF/DMA to give the *N,N*-dimethylaminomethylenehydrazono derivative **520**, which thermally cyclized to the



SCHEME 100



SCHEME 101

1,2,4-triazolo[4,3-*c*]pyrimidine **521**, which immediately rearranged into **458** (85GEP3427823; 90JMC1230) (Scheme 101).

Isomerization of the triazolo[4,3-*c*]pyrimidines **522**, **524**, and **528** to their corresponding [1,5-*c*]isomers **523**, **525**, and **529** took place on heating in methanol (81USP4269980), formic acid, or ethyl formate, respectively (84-EUP121341; 86USP4591588; 94JMC2371). Similarly, **526**, **530**, and **532** were isomerized to **527**, **531**, and **533**, respectively by heating (86TL3127), by alkali (94JMC2371), and by the action of sodium ethoxide (92KGS225; 93KGS1545; 95MIP2, 95MIP3).

Apparently triazolo[4,3-*c*]pyrimidine rearranges readily into the more stable isomer triazolo[1,5-*c*]pyrimidine. A detailed study on related systems showed that electronic and steric factors are mainly responsible for this rearrangement (78AJC2505; 90T3897; 92KGS225) (Scheme 102).

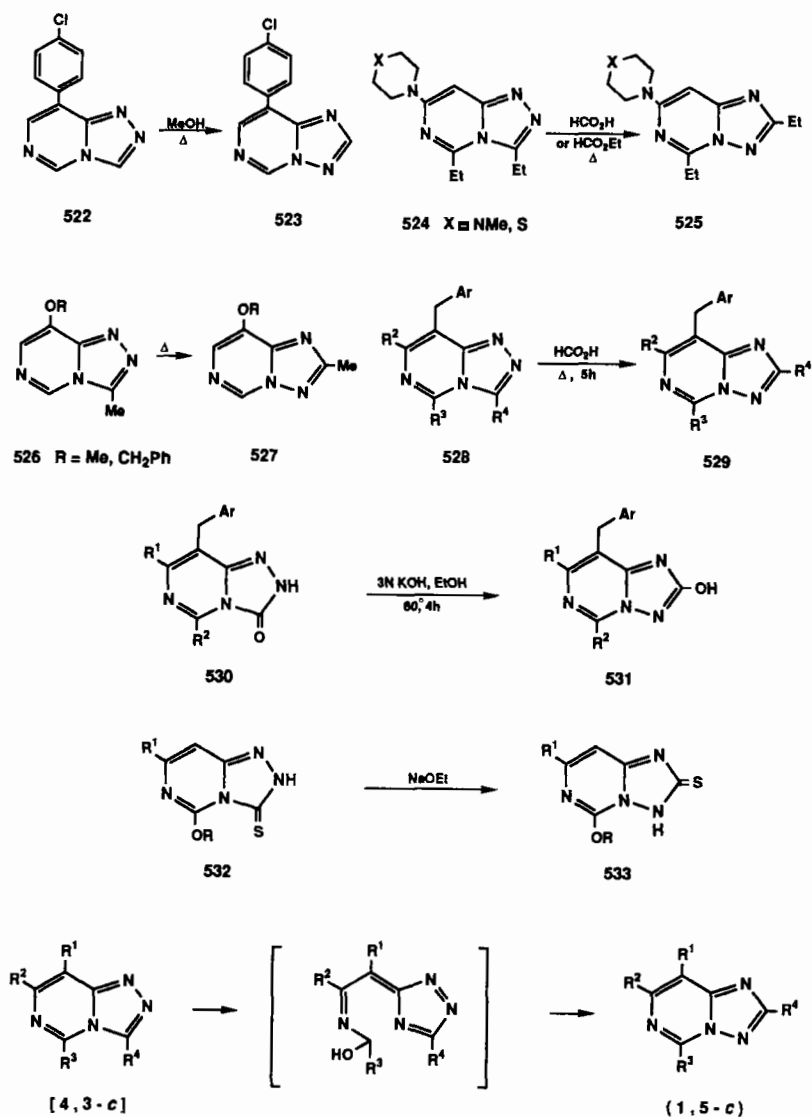
## 5. Reactivity

A prototropic allylic rearrangement took place during the Dimroth rearrangement of 8-allyl-5-benzyl-7-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine (**534**) to give 5-benzyl-7-methyl-8-propenyl-1,2,4-triazolo[1,5-*c*]pyrimidine (**535**) on heating with NaOEt (93KGS1545) (Scheme 103).

Treatment of **533** with  $\text{H}_2\text{O}_2/\text{MeOH}$  gave the disulfide **536**, whose chlorination gave the chlorosulfonyl derivative **537** (95MIP3) (Scheme 104).

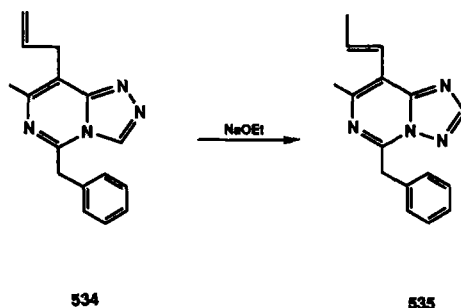
Catalytic hydrogenation of **484** afforded the diaminotriazolopyrimidine **538**, which upon reaction with the appropriate fluorophenylacetyl chloride gave an acylamino derivative whose ring closure with polyphosphoric acid gave the triazolopurine **539** (94JHC1171) (Scheme 105).

When 8-ethoxyethyl-7-phenyltriazolopyrimidinamine (**542**) was diazo-

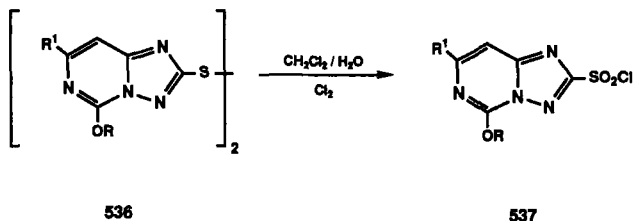


SCHEME 102

tized in the presence of HCl and hydrolyzed, it gave the corresponding 5-chloro derivative, which was heated in DMSO with  $\text{NaN}_3$  to give a mixture of the tetrazolo[1,5-*a*]triazolo[1,5-*c*]pyrimidine **541** and its tautomeric



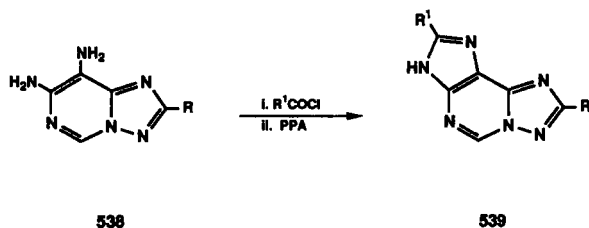
SCHEME 103



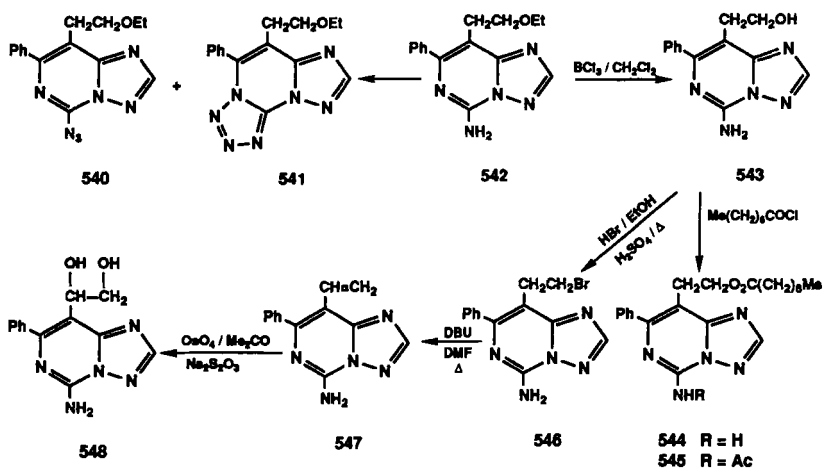
SCHEME 104

azide **540** (86EUP152841). Reaction of **542** with boron trichloride gave the hydroxyethyl derivative **543**, whose acylation with octanoyl chloride gave **544**, which was acetylated to **545** (84USP4483987). Heating **543** with HBr in ethanol containing sulfuric acid afforded the bromo derivative **546**. Elimination of hydrogen bromide from **546** by heating with DBU in DMF led to the vinyl derivative **547**, whose hydroxylation with OsO<sub>4</sub> gave 5-amino-8-(1,2-dihydroxyethyl)-7-phenyl-1,2,4-triazolo[1,5-*c*]pyrimidine (**548**) (89USP4866063) (Scheme 106).

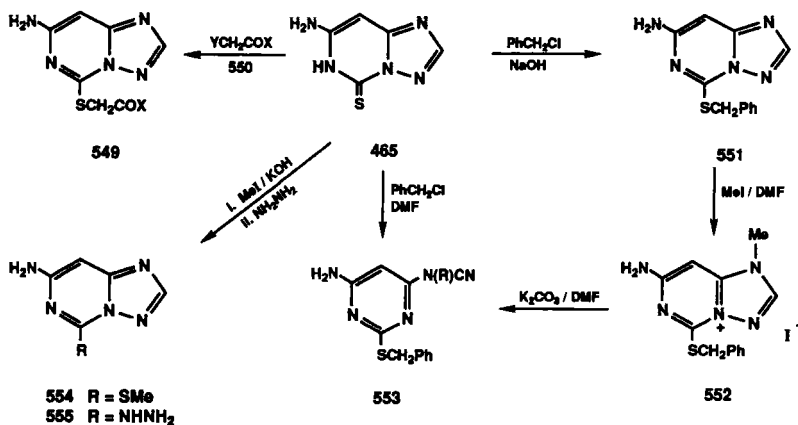
Alkylation of thione **465** with **550** gave **549** (92KFZ30). Benzylation of **465** with benzyl chloride and NaOH gave **551**, whose methylation with MeI in DMF gave the quaternary salt **552**; subsequent treatment with K<sub>2</sub>CO<sub>3</sub> in DMF gave **553** (R = Me) via an aminonitrile rearrangement. Heating **465** with benzyl chloride in DMF gave **553** (R = Bn) (85KGS421). Methylation of **465** with MeI/KOH followed by reaction with hydrazine gave **554** and **555**, respectively (79KGS262). Methylation of 2-hydroxytriazolo[1,5-*c*]pyrimidines (**492**) with MeI/MeONa/MeOH provided **556** (85USP4528288) (Scheme 107).



SCHEME 105



SCHEME 106



SCHEME 107

Chlorination of thiobenzyl derivative **494** led to **557**, whose reaction with aromatic amines afforded the *N*-aryl-1,2,4-triazolo[1,5-*c*]pyrimidine-2-sulfonamide **558** (89EUP343752; 93USP5177206).

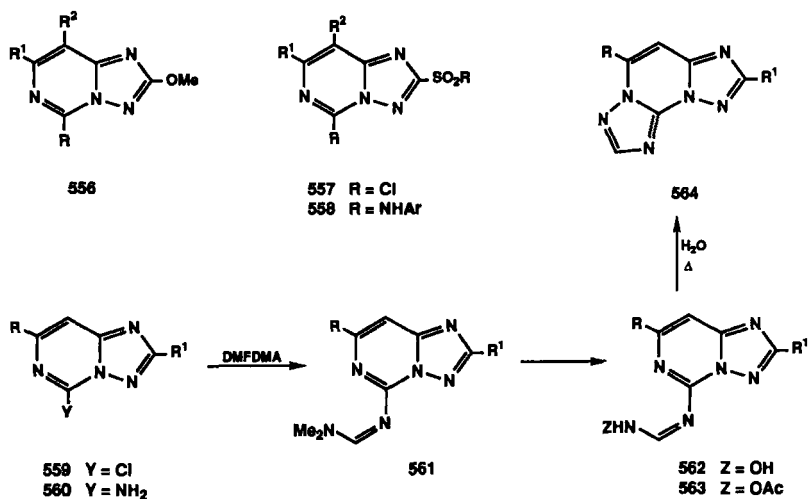
A general synthetic route to the tricyclic system bis-1,2,4-triazolo[1,5-*a*:1',5'-*c*]pyrimidine **564** was carried out by converting the triazolopyrimidinone **501** with  $\text{POCl}_3$  into the corresponding chloro derivative **559**, whose reaction with ammonia then gave the amine **560**. With DMF/DMA, **560** gave Schiff bases **561**, which underwent successive transformation by hydroxylamine and *O*-acetylation to furnish **562** and **563**, respectively. On boiling in water, the latter gave **564** (80AJC1147) (Scheme 108).

1,2,4-Triazolo[1,5-*c*]pyrimidin-5(6*H*)-one nucleosides (**565**) were prepared by coupling the sugar derivatives with triazolopyrimidinones (89JIC686) (Scheme 109).

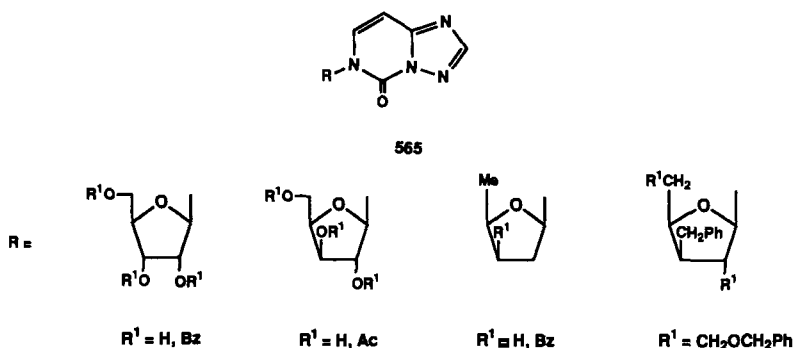
## 6. Biological Properties

Compounds **492** caused 75% relaxation of histamine-induced contraction (85USP4528288). Compounds **495–497** are a new class of bicyclic antagonists that produced a potent, oral antihypertensive activity (94-JMC2371).

Compounds **523** were prepared as bronchodilators (84EUP121341; 86USP4591588), and **540** and **541** increased renal blood flow and urine



SCHEME 108



SCHEME 109

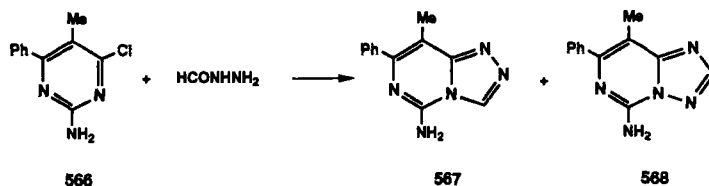
output (86EUP152841); **549** ( $X = \text{OH}$ ) inhibited sarcoma and possessed viricidal and radioprotective activities (92KFZ30). Nucleosides **565** inhibited the growth of amastigotes of *Leishmania donovani* in hamster (89JIC686).

#### D. 1,2,4-TRIAZOLO[4,3-*c*]PYRIMIDINES

##### 1. Synthesis from Pyrimidines

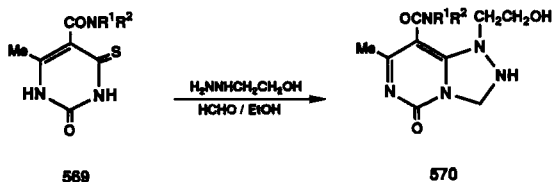
Reaction of 4-chloro-5-methyl-6-phenyl-2-pyrimidinamine (**566**) with formylhydrazine yielded a mixture of triazolo[4,3-*c*]pyrimidine (**567**) and its [1,5-*c*]isomer **568** (83USP4405780), and boiling **566** with formylhydrazine in DMF containing a 3-Å molecular sieve afforded **567** (81GEP3029871) (Scheme 110).

The thioxopyrimidinecarboxamides (**569**) were condensed with (2-hydroxyethyl)hydrazine, followed by reaction with aqueous ethanolic formaldehyde to give 1-(2-hydroxyethyl)triazolo[4,3-*c*]pyrimidines (**570**) (92PJC131) (Scheme 111).



SCHEME 110





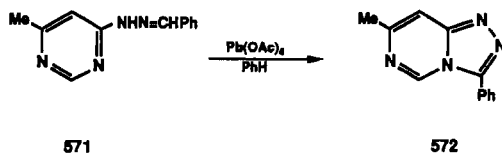
SCHEME 111

Cyclization of the hydrazone **571** by the action of lead tetraacetate in benzene afforded the triazolo[4,3-*c*]pyrimidine **572** (57JCS727) (Scheme 112).

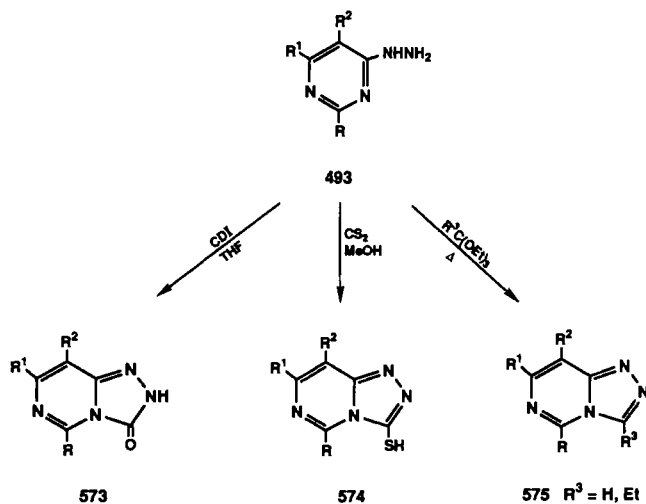
Treatment of the ethoxycarbonyl derivative **502** with phosphoryl chloride gave the triazolo[4,3-*c*]pyrimidinone **505**. The same product was formed with a trace of the isomeric triazolo[1,5-*c*]pyrimidine **504** when **502** was boiled with *o*-dichlorobenzene. Compound **505** also was obtained by reacting a solution of hydrazine **493** ( $R^2 = \text{H}$ ) in dry toluene with phosgene (65JCS3357). Similarly, **493** gave a series of products: **573** by reaction with 1,1'-carbonyldiimidazole (94JMC2371), **574** on reaction with carbon disulfide (89JHC313; 94JMC2371; 95MIP4), and **575** by reaction with an orthoester (84EUP121341; 85USP4532242; 86USP4591588) (Scheme 113).

7-Methyl-5-oxo-1,5-dihydro-8-carbamoyl-1,2,4-triazolo[4,3-*c*]pyrimidines **577** and **578** were prepared by the cyclization of **576** with acetic anhydride and ethyl oxalate, respectively (89PHA604). The 4-methyl-1,2-dihydropyrazolo[3,4-*d*]pyrimidine-3,6-dione **579** also was obtained in the latter case, as a consequence of breaking the amide bond and releasing the amine moiety. Coupling ethyl dithioacetate and 5-chloro-4-hydrazinopyrimidine (**580**) afforded the triazolo[4,3-*c*]pyrimidine **581** (89H239) (Scheme 114).

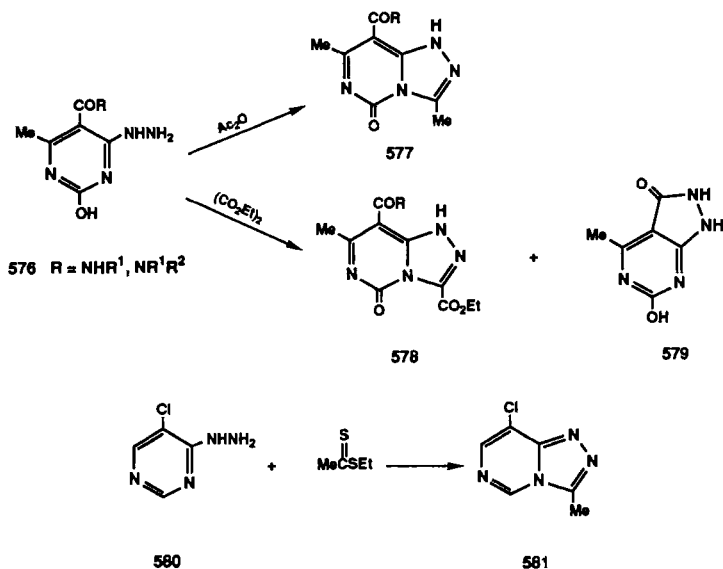
8-Alkoxy-1,2,4-triazolo[4,3-*c*]pyrimidines were obtained by condensing 5-alkoxy-4-hydrazinopyrimidines with triethyl orthoacetate (86TL3127; 89JHC687) or triethyl orthoformate (91AKZ448; 94JMC2371). The 1,2,4-triazolo[4,3-*c*]pyrimidine **584** was prepared by the cyclocondensation of 5-(4-chlorophenyl)-4-hydrazinopyrimidine (**582**) with acetal **583** (81 USP4269980) (Scheme 115).



SCHEME 112

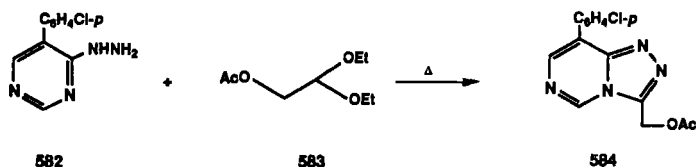


SCHEME 113



SCHEME 114

Phosgenimium chlorides (**585**) permit a regiospecific synthesis of 3-(di-substituted amino)triazolo[4,3-*c*]pyrimidines (**588**) from the 4-hydrazinopyrimidine **488** without a Dimroth type of rearrangement



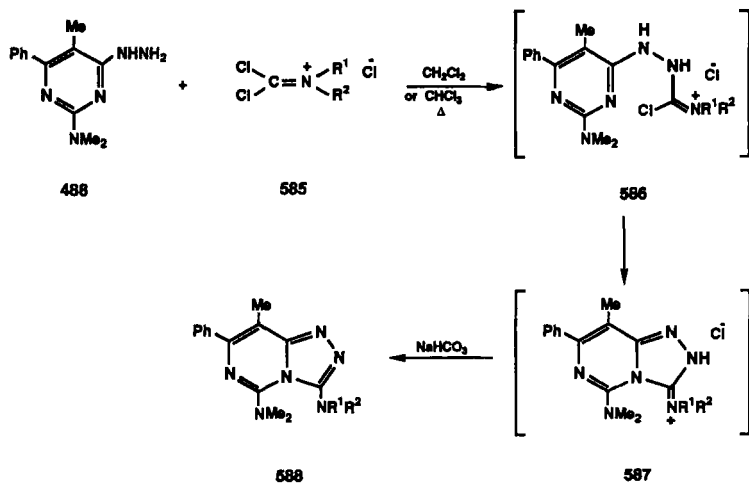
SCHEME 115

(90T3897). *N,N*-Dibenzylphosgenimium salt **585** ( $R^1 = R^2 = \text{CH}_2\text{Ph}$ ) led to 3-benzylaminotriazolopyrimidine **588** ( $R^1 = \text{H}$ ,  $R^2 = \text{CH}_2\text{Ph}$ ) via the loss of benzyl chloride from the intermediate **586** or **587** (Scheme 116).

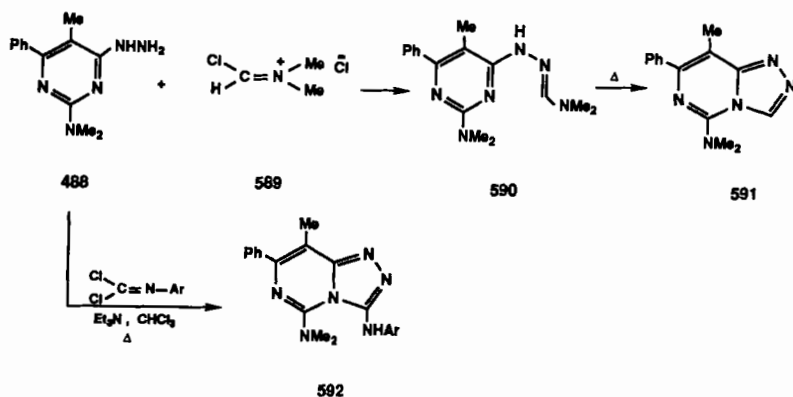
Thermolysis of the formamidrazone **590**, obtained from the reaction of hydrazine **488** with Vilsmeier salt **589**, at  $200^\circ\text{C}$  or on boiling in nitrobenzene led, by intramolecular transformation, to the triazolo[4,3-*c*]pyrimidine **591** (90T3897). Aryl isocyanide dichlorides reacted with **488** in the presence of  $\text{Et}_3\text{N}$  to give 3-anilinotriazolopyrimidines (**592**) (Scheme 117).

The synthesis of the nucleoside **594** was performed by the reaction of the hydrazino derivatives **593** with acetic anhydride at room temperature. Deacetylation of **594** gave (2-deoxy- $\beta$ -D-ribofuranosyl)triazolopyrimidine (**595**). Reaction of **593** with acetic formic anhydride in dry pyridine followed by treatment with ammonia/MeOH gave the triazolo[4,3-*c*]pyrimidine nucleoside **596** (91MI4) (Scheme 118).

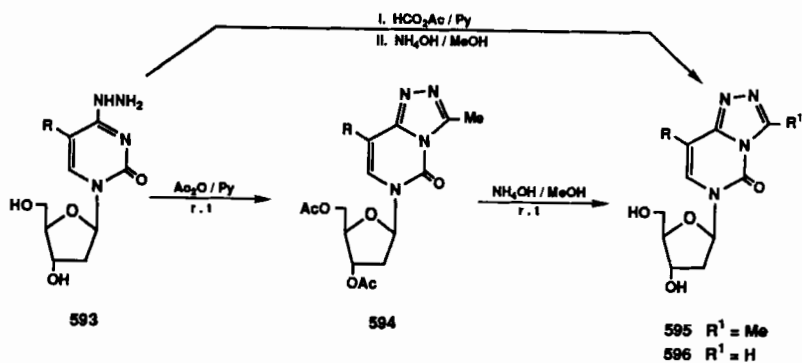
Hydrogenation of the antibiotic reumycin **597** over  $\text{PtO}_2$  in acetic anhy-



SCHEME 116



SCHEME 117

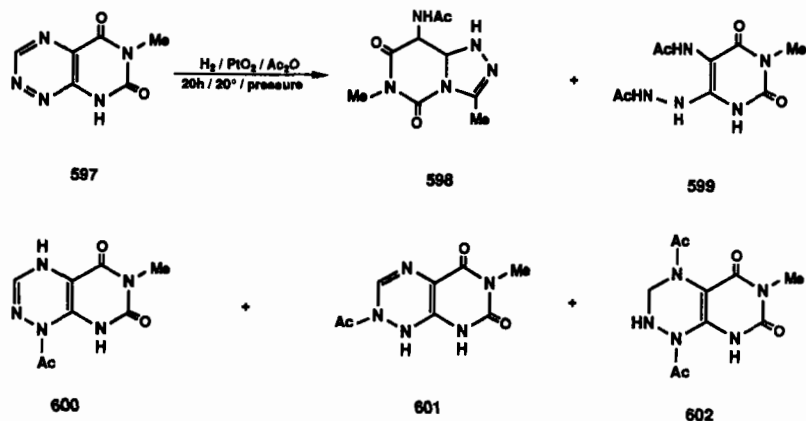


SCHEME 118

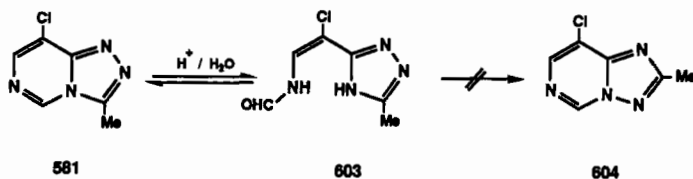
dride at 20°C and atmospheric pressure gave a mixture of the acetyl derivatives of triazolopyrimidinedione (**598**), pyrimidinedione (**599**), and pyrimidiotriazinediones (**600–602**) (81KPS85) (Scheme 119).

## 2. Reactivity

Hydrogenolysis of 8-benzyloxy-3-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine gave the corresponding 8-hydroxy derivative (86TL3127; 89JHC687). 8-Chlorotriazolopyrimidine (**581**) underwent a reversible ring opening to afford triazole **603** upon treatment with acids. The latter on pyrolysis gave the starting base **581** rather than the rearranged [1,5-*c*]isomer **604** (89H239) (Scheme 120).



SCHEME 119



SCHEME 120

### 3. Biological Properties

Amine **567** and its amides are useful diuretics (81GEP3029871). Compound **570** has antiarrhythmic activity (92PJC131). Compounds **573–575** were prepared as potent, active angiotensin II receptor antagonists (94JMC2371).

## III. Tetrazolo[*x,y-z*]pyrimidines

Two possible isomeric structures, [1,5-*a*] and [1,5-*c*], are relevant for this ring. Both have a bridgehead nitrogen atom and have a carbon–nitrogen bond at the site of fusion (Scheme 121).

### A. TETRAZOLO[1,5-*a*]PYRIMIDINES

#### 1. Synthesis from Pyrimidines

This group is generally prepared by the action of nitrous acid on a suitable hydrazinopyrimidine. Here, **605** afforded the respective tetrazolopy-

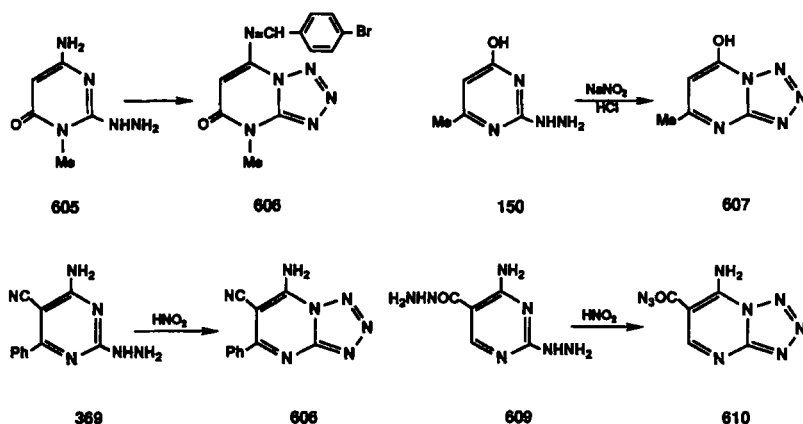


SCHEME 121

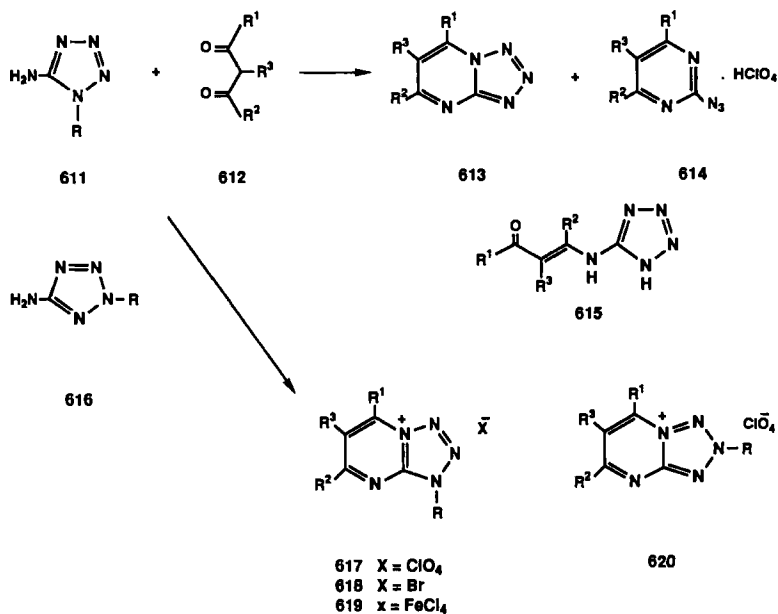
rimidine, isolated as its *p*-bromobenzylidene derivative **606** (90MI3); there is only one possible site for the cyclization. Reaction of the 2-hydrazino pyrimidine **150** with  $\text{NaNO}_2/\text{HCl}$  gave the tetrazolo derivative **607** and not its isomeric analog (57JCS727). Similarly, 2-hydrazino-4-amino-5-cyano-6-phenylpyrimidine (**369**) gave 5-phenyl-6-cyano-7-aminotetrazolo[1,5-*a*]pyrimidine (**608**) as the most probable structure [83ZN(B)1686], and **609** gave 7-amino-6-azidocarbonyltetrazolo[1,5-*a*]pyrimidine (**610**) (86H1899) (Scheme 122).

## 2. Synthesis from 5-Aminotetrazoles

Cyclocondensation of 5-aminotetrazoles with 1,3-dicarbonyl compounds is generally a method for the synthesis of tetrazolopyrimidines. The reaction of **612** with **611** ( $\text{R} = \text{H}$ ) gave the tetrazolopyrimidine **613** or the azidopyrimidine **614** depending on the reaction conditions. In  $\text{AcOH}$ , the tetrazolopyrimidine **613** was formed exclusively, but the  $\beta$ -ketoamine **615** was obtained along with **613** in absolute  $\text{EtOH}$  [93IJC(B)886]. Cyclocondensation of the substituted aminotetrazoles **611** or **616** with  $(\text{EtO})_2\text{CH}_2\text{CH}_2$ ,  $\text{R}^1\text{COCH}_2\text{COR}^2$ , or  $\text{R}^2\text{COCR}^3=\text{CHCl}$  in the presence of  $\text{HClO}_4$ ,  $\text{HBr}$ , or  $\text{FeCl}_3$  afforded the corresponding quaternary tetrazolo[1,5-*a*]pyrimidinium salts **617–619** and **620**, respectively, whose subsequent condensation



SCHEME 122



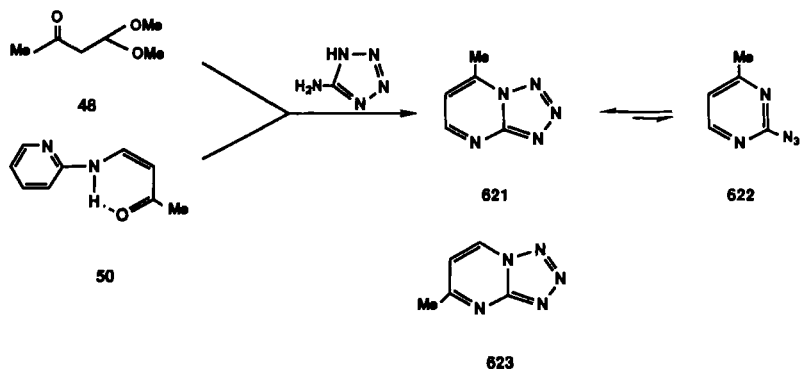
SCHEME 123

with *p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CHO, when R<sup>3</sup> = Me, gave the corresponding dyes (87 UKZ319) (Scheme 123).

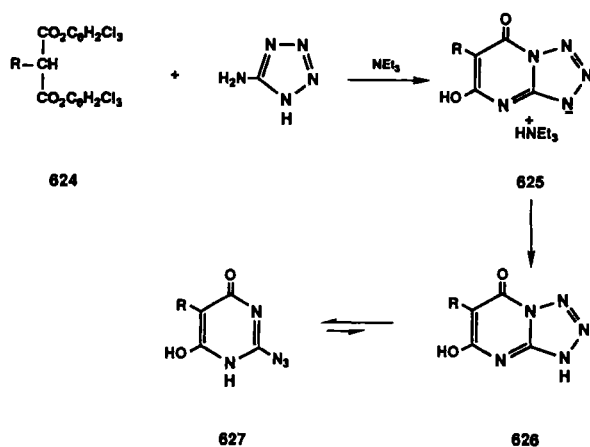
The structure **623** was given to the product formed from the reaction of 5-aminotetrazole with ethyl acetoacetate, and subsequent treatment with phosphoryl chloride and then hydrogenolysis (59JOC796). Alternatively, reactions of 4-methyl-2-hydrazinopyrimidine with nitrous acid, or 5-aminotetrazole with the ketoacetal **48** gave **623** (59JOC796). However, the spectroscopic properties of the condensation product were consistent with structure **621** rather than **623** and indicated that it exists in equilibrium with the azido form **622** with a 3:1 ratio of **621** to **622**. Treatment of 2-(2-acetylvinylamino)pyridine **50** with 5-aminotetrazole gave **621** [79JCS(P1)3085] (Scheme 124).

Reaction of bis(2,4,6-trichlorophenyl)malonates (**624**) with 5-aminotetrazole in the presence of Et<sub>3</sub>N yielded the ammonium salts **625**. Upon treatment of **625** with strong acids, a mixture of **626** and the 2-azidopyrimidines (**627**) was obtained (93JHC1267) (Scheme 125).

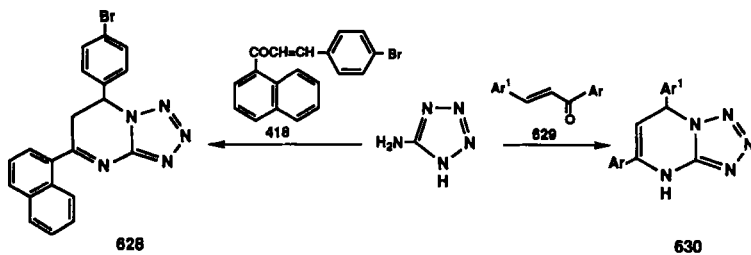
Condensation of the chalcones **418** and **629** with 5-aminotetrazole afforded the 6,7-dihydrotetrazolo[1,5-*a*]pyrimidine **628** (89PHA820) and the 4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **630** (88KGS1489), respectively (Scheme 126).



SCHEME 124

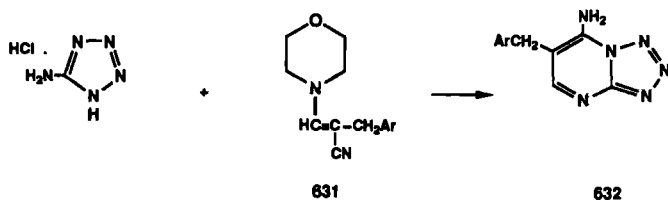


SCHEME 125



SCHEME 126





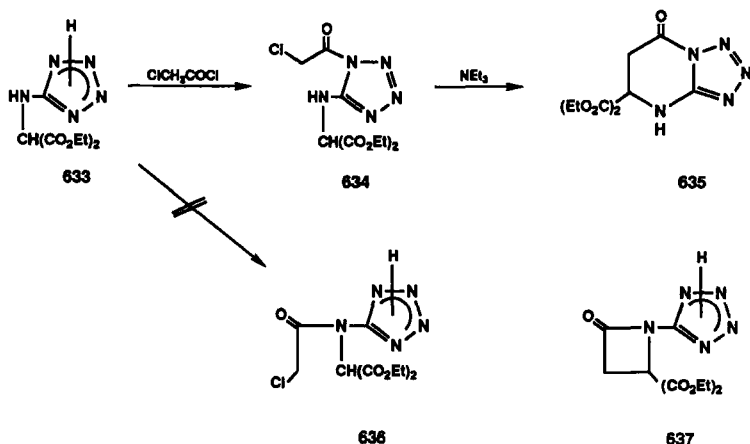
SCHEME 127

The tetrazolo[1,5-*a*]pyrimidines **632** were formed by cyclocondensation of  $\beta$ -morpholino- $\alpha$ -(3,4,5-trimethoxybenzyl)acrylonitriles (**631**) with 5-aminotetrazole hydrochloride (85INP155606) (Scheme 127).

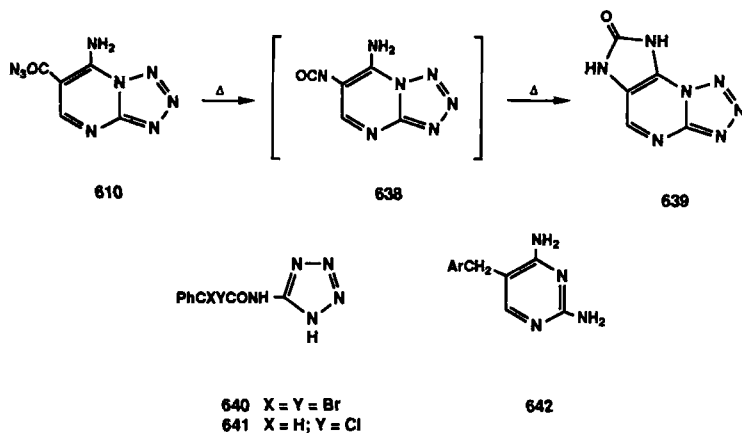
The synthesis of the 4,5,6,7-tetrahydrotetrazolo[1,5-*a*]pyrimidine ring started by reacting 5-aminotetrazole with diethyl bromomalonate to afford diethyl(tetrazol-5-ylamino)malonate (**633**), whose chloroacetylation led to the formation of **634** rather than **636**. Treatment with triethylamine induced ring closure of the chloroacetyl derivative to afford the tetrazolo[1,5-*a*]pyrimidine **635** rather than the isomer **637** (93ACH683) (Scheme 128).

### 3. Reactivity

Compound **610** was transformed thermally to the tetrazolo[5,1-*b*]purin-7(8*H*)-one **639** through Curtius rearrangement via the isocyanate intermediate **638** (86H1899). Reaction of **626** (R = Ph) with bromine or sulfuryl chloride led by ring opening and decarboxylation to the halogenated tetra-



SCHEME 128



SCHEME 129

zole derivatives **640** or **641**, respectively (93JHC1267). Hydrogenation of **632** with Raney Ni gave the diaminopyrimidine **642** (85INP155606) (Scheme 129).

#### 4. Physicochemical Data

Chemical reactivity and NMR spectroscopy suggested that the tetrazolopyrimidines with a bridgehead nitrogen are planar and possess a high degree of aromatic character (80PAC1611).  $^1\text{H}$  and  $^{13}\text{C}$  NMR study of 2-azido-4-methylpyrimidine (**622**) indicated that it exists in tautomeric equilibrium with two tetrazole forms, **621** and **623**. The ratio is dependent on the polarity of the solvent. In the crystal state, **621** was found to be the exclusive tautomer, reflecting the relationship between the tetrazole stability and the electron-donating group at position 5. The kinetics of tautomerization

**621**  $\xrightleftharpoons[k_2]{k_1}$  **622**  $\xrightleftharpoons[k_4]{k_3}$  **623** (90KGS1648), and the tautomerism of **628** and **630** to their 4,7- and 6,7-dihydro derivatives, respectively, were studied (88KGS1489).

Tetrazolo[1,5-*a*]pyrimidines (**643**) with electron-donating groups in position 5 showed no pronounced tendency to tautomerize to azides. An electron-withdrawing group in position 5, by contrast, favors the azido form **644**, which is a metastable solid at room temperature, rearranging to tetrazole **643** at the melting point; the azide is formed again when the tetrazole melts. Contrary to general belief, 2,4-diazidopyrimidines exist in the 5-azidotetrazol[1,5-*a*]pyrimidine form **643** ( $\text{R}^3 = \text{N}_3$ ), with the isomeric 5-

azidotetrazolo[1,5-*c*]pyrimidine form **645** as a minor constituent. The diazido form **644** ( $R^3 = N_3$ ) is metastable at room temperature, rearranging to both tetrazoles at the melting point. Liquid  $SO_2$  was found to be a suitable solvent for preserving individual tautomers in solution (65JOC826; 70T4915, 70T4969). NMR results indicated that the diazidopyrimidines **647** coexist in solution with their mono- (**646**) and bistetrazole (**648**) tautomers (86IZV1916) (Scheme 130).

Compound **613** ( $R^1 = R^2 = H$ ;  $R^3 = 2\text{-adamantyl}$ ) has peculiar properties due to the presence of the lipophilic group. It exhibits a solvent-dependent tetrazolo–azido valence isomerization [82ZN(B)1187].

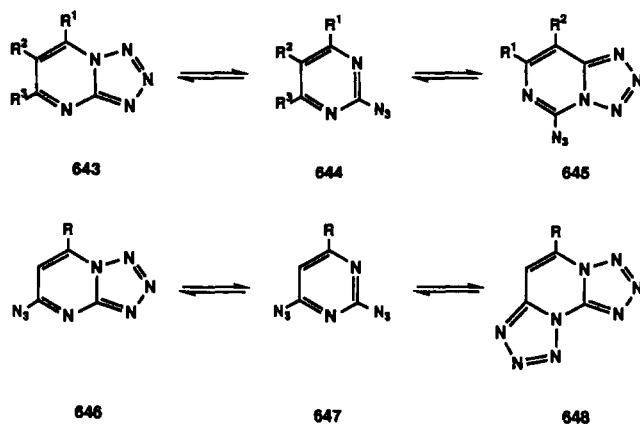
### 5. Uses and Biological Properties

The condensation products of the quaternary tetrazolo[1,5-*a*]pyrimidinium salts **617–620** ( $R^3 = Me$ ) with  $p\text{-Me}_2NC_6H_4CHO$  are used as dyes (87UKZ319). Compound **628** has antifungal activity (89PHA820).

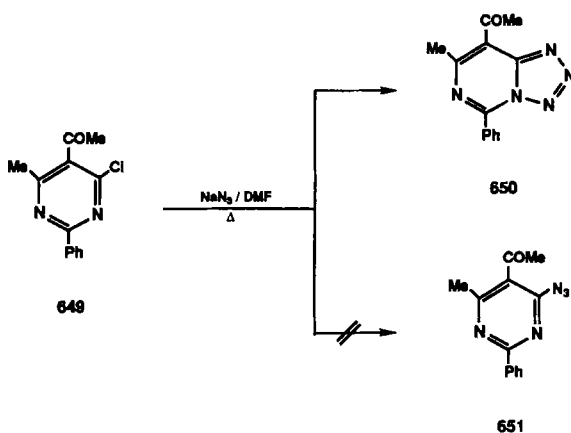
## B. TETRAZOLO[1,5-*c*]PYRIMIDINES

### 1. Synthesis from Pyrimidines

The tetrazolo[1,5-*c*]pyrimidine **650** was prepared by boiling the chloropyrimidine **649** with sodium azide in DMF; the tautomeric azidopyrimidine **651** was not formed (91PHA26) (Scheme 131).



SCHEME 130

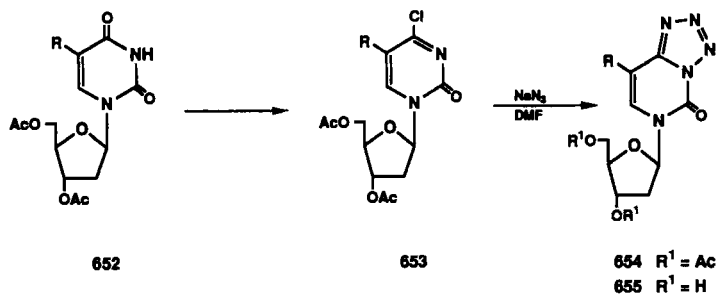


SCHEME 131

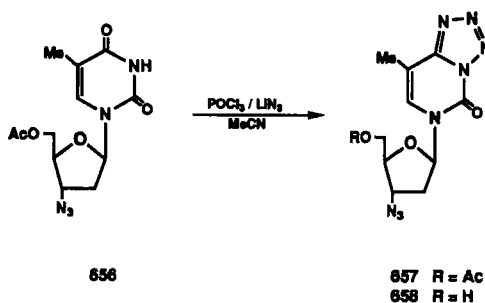
Conversion of the 3',5'-diacetyl thymidine **652** ( $\text{R} = \text{Me}$ ) to the chloro derivative **653** followed by reaction with sodium azide in anhydrous DMF gave **654**, whose hydrolysis gave **655** (86JHC1401). The 2'-deoxy-2',2'-difluoro analog of **655** was prepared (93EUP576230) (Scheme 132).

The 3'-azido-3'-deoxythymidine **656** was converted to the tetrazolo[1,5-*c*]pyrimidinone nucleoside **657** by treatment with  $\text{POCl}_3/\text{LiN}_3$  in MeCN. Reaction of **657** with  $\text{NH}_3/\text{MeOH}$  gave **658** (92BBR1545) (Scheme 133).

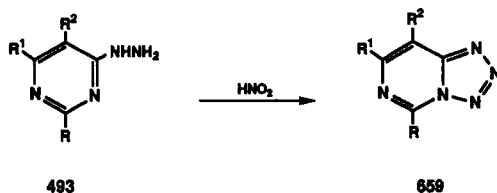
Alternatively, reaction of hydrazinopyrimidine **493** with nitrous acid afforded the tetrazolopyrimidines **659** (89JHC313; 91AKZ448; 92MI5) (Scheme 134).



SCHEME 132



SCHEME 133



SCHEME 134

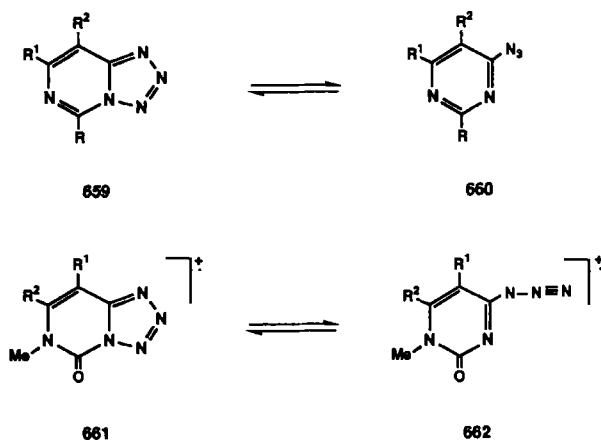
## 2. Physicochemical Data

In the tetrazolo[1,5-*c*]pyrimidine/4-azidopyrimidine series **659/660**, the opposite effect to the [1,5-*a*] analog has been observed, whereby electron-donating groups in positions 5 and 7 stabilize the azido form **660** but in position 8 favor the tetrazole form **659** (65JOC826). The tetrazole form of this ring is somewhat less stable than that in tetrazolo[1,5-*a*]pyrimidine (65JOC826; 65JOC829; 73S123).

Mass fragmentation of modified nucleobases of 6-methyl tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one and its 7 and 8-methyl derivatives suggested the occurrence of both azide and tetrazole tautomeric forms of  $M^+$  (**661** and **662**). For the 8-halo derivatives, only the  $M^+$  of the tetrazole form was proposed (93OMS643) (Scheme 135).

## 3. Biological Properties

2'-Deoxy-2',2'-difluoro analogs of **655** have antiviral and anticancer activity (93EUP576230).



SCHEME 135

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67JCS(C)503  
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69CRV345  
70CB3266  
70T4915  
70T4969  
71CB2702  
  
71JHC237  
  
73JHC1069  
  
73S123  
73TL1677  
  
74JCS(CC)486  
  
74JOC1256  
  
74JOC2143  
  
74JOC3226  
  
74TL129  
  
75JHC107  
  
75JHC1187  
  
76JCS(P1)2166  
  
76S833  
77AJC2515  
77HC188  
  
77MI1  
  
78AJC2505  
78MI1  
  
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# Chemistry of Pyrido[2,1-*b*][1,3]oxazines, Pyrido[2,1-*b*][1,3]thiazines, and Their Benzologs, Part IV

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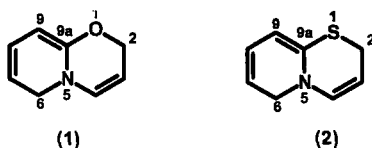
I. Introduction .....	225
II. Structure .....	226
A. Pyrido[2,1- <i>b</i> ][1,3]oxazines and Their Benzo Derivatives .....	226
B. Pyrido[2,1- <i>b</i> ][1,3]thiazines and Their Benzo Derivatives .....	233
III. Reactivity .....	234
A. Pyrido[2,1- <i>b</i> ][1,3]oxazines and Their Benzo Derivatives .....	234
B. Pyrido[2,1- <i>b</i> ][1,3]thiazines and Their Benzo Derivatives .....	243
IV. Synthesis .....	253
A. Pyrido[2,1- <i>b</i> ][1,3]oxazines and Their Benzo Derivatives .....	253
B. Pyrido[2,1- <i>b</i> ][1,3]thiazines and Their Benzo Derivatives .....	264
V. Applications and Important Compounds .....	271
A. Pyrido[2,1- <i>b</i> ][1,3]oxazines and Their Benzo Derivatives .....	271
B. Pyrido[2,1- <i>b</i> ][1,3]thiazines and Their Benzo Derivatives .....	275
References .....	275

## I. Introduction

The chemistry of the pyrido[2,1-*b*][1,3]oxazines (**1**), pyrido[2,1-*b*][1,3]thiazines (**2**) (Scheme 1), and their benzologs (**3**)–(**12**) (Schemes 2 and 3) has not been systematically reviewed.

In the present article the primary chemical literature up to the end of 1997 has been surveyed the Subject and Chemical Substance indexes of *Chemical Abstract* up to and including Volume 126 have been searched.

The perhydropyrido[2,1-*b*][1,3]oxazine skeleton is a constituent part of macrocyclic xestospongine/araguspongine and aragupetrosine alkaloids isolated from different marine sponges. Pyrido[2,1-*b*][1,3]oxazines, pyrido[2,1-*b*][1,3]thiazines, and [1,3]oxazino[3,4-*a*]quinolines are also applied as key intermediates in the total syntheses of different alkaloids. Other examples of these ring systems have aroused much interest owing to their valuable pharmacological properties.



SCHEME 1

In the following sections the physicochemical and spectroscopic properties, reactions, syntheses, and, more briefly, utilization of these ring systems are discussed. Within the individual sections the pyrido[2,1-*b*][1,3]oxazines and their benzologs and pyrido[2,1-*b*][1,3]thiazines and their benzologs are dealt with.

## II. Structure

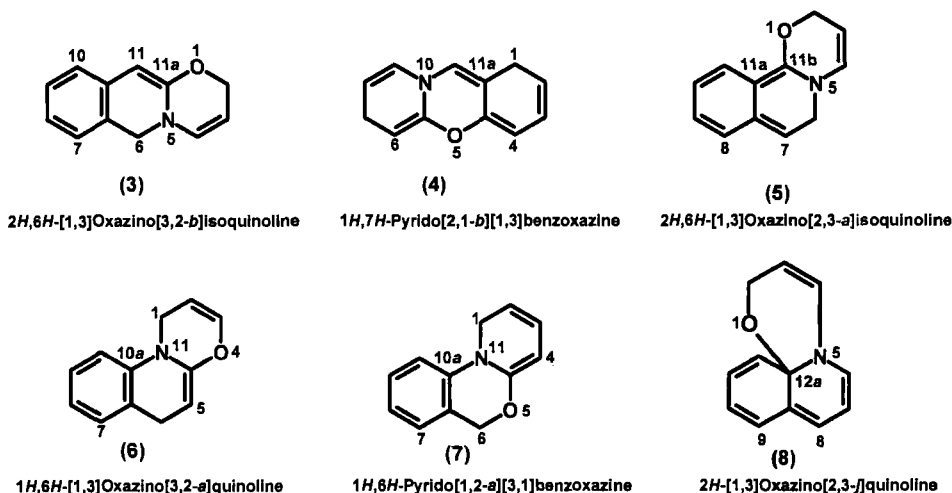
### A. PYRIDO[2,1-*b*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. *Thermodynamic Aspects*

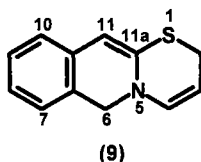
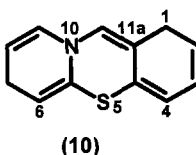
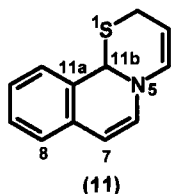
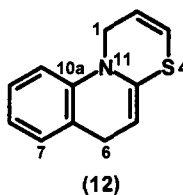
The polarographic behavior of 5*a*-hydroxy-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-11-one has been investigated (67IZV1952).

9,10-Dimethoxy-2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinoline

#### Benzo Derivatives of Pyrido[2,1-*b*][1,3]oxazine



SCHEME 2

Benzo Derivatives of Pyrido[2,1-*b*][1,3]thiazine2*H*,6*H*-[1,3]Thiazino[3,2-*b*]isoquinoline1*H*,7*H*-Pyrido[2,1-*b*][1,3]benzothiazine2*H*,6*H*-[1,3]Thiazino[2,3-*a*]isoquinoline1*H*,6*H*-[1,3]Thiazino[3,2-*a*]quinoline

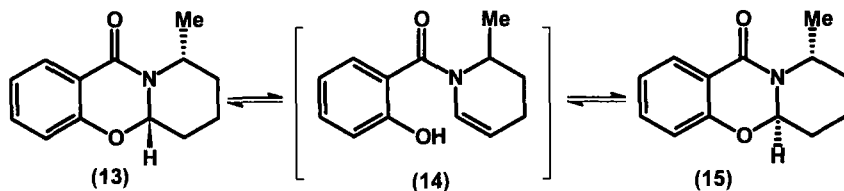
SCHEME 3

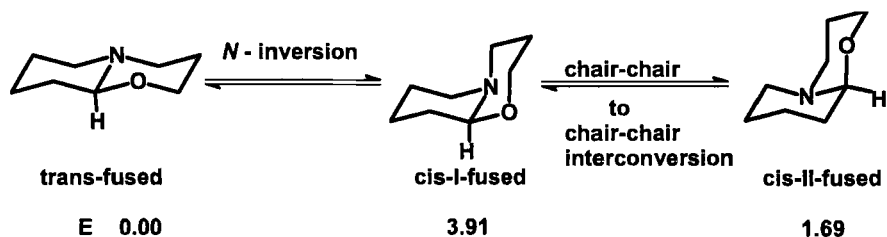
in 66% aqueous dimethylformamide has a  $pK_a$  of 8.40 (66AP817). The  $pK_a$  value of *cis*-2,9*a*-*H*-2-hydroxymethylperhydropyrido[2,1-*b*][1,3]oxazine hydrochloride was determined to be  $7.69 \pm 0.02$  in aqueous solution (95JOC2989).

Ring-chain tautomerism involving the heterorings must be considered in the reactions of 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines (66AP817; 86AJC893). Acid-catalyzed epimerization of 9-methylhexahydropyrido[2,1-*b*][1,3]-benzoxazin-11-ones (**13**) and (**15**) occurred via the enamine form of the chain tautomer **14** to give an 1:94 equilibrium mixture of **13** and **15** (89TL7321).

## 2. Theoretical Calculations

Hoye *et al.* carried out force-field calculations on the different conformations of all the diastereomers of perhydropyrido[2,1-*b*][1,3]oxazine and its

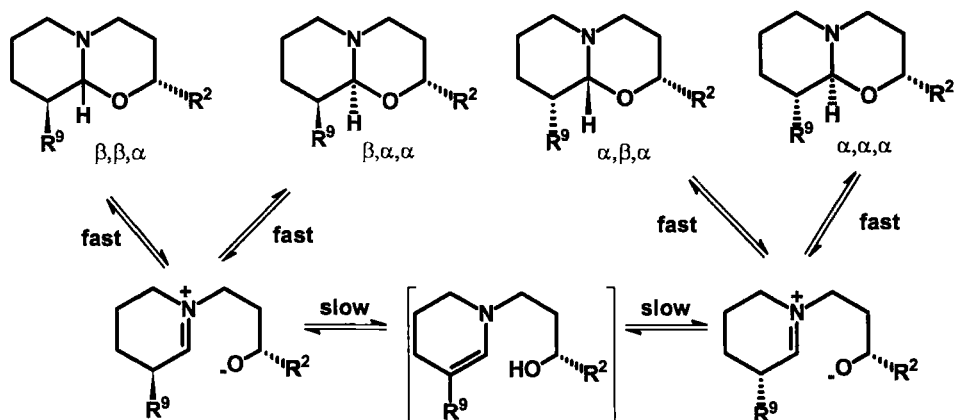




SCHEME 4. The most stable conformations of perhydropyrido[2,1-*b*][1,3]oxazine. The numbers indicate the energy ( $\text{kcal} \cdot \text{mol}^{-1}$ ) relative to the most stable species. The *cis*-II-fused conformer is considerably less stable.

2-, 6-, and 9-methyl and 2,9-dimethyl derivatives (90TL4281; 94JOC6904). In these calculations, it was taken into consideration that, besides N-inversion (between the *trans*-fused and *cis*-fused conformations) and chair-chair to chair-chair interconversion (between the two *cis*-fused conformations) (Scheme 4), ring-chain and iminium-enamine tautomerizations also take place (Scheme 5). Monte Carlo conformational searches were performed on each conformation, and in each case the global minimum was found when both six-membered rings were in chairlike conformations. The minimum was substantially below the next lowest energy conformer, which always had at least one ring in a distorted, nonchair conformation. Boltzmann analysis of the energies for the *trans*, *cis*-I, and *cis*-II-fused conformations for each diastereomer in chloroform led to the calculated equilibrium distribution for all species (see Fig. 1 as an example).

MM2 force-field calculations were used to estimate the relative energies



SCHEME 5. Ring-chain and iminium-enamine tautomerism for the interconversion of perhydropyrido[2,1-*b*][1,3]oxazines.  $\alpha$  and  $\beta$  refer to the "down" vs. "up" orientation, respectively, of the alkyl substituents on C-2 and C-9 and of the hydrogen atom on C-9a.

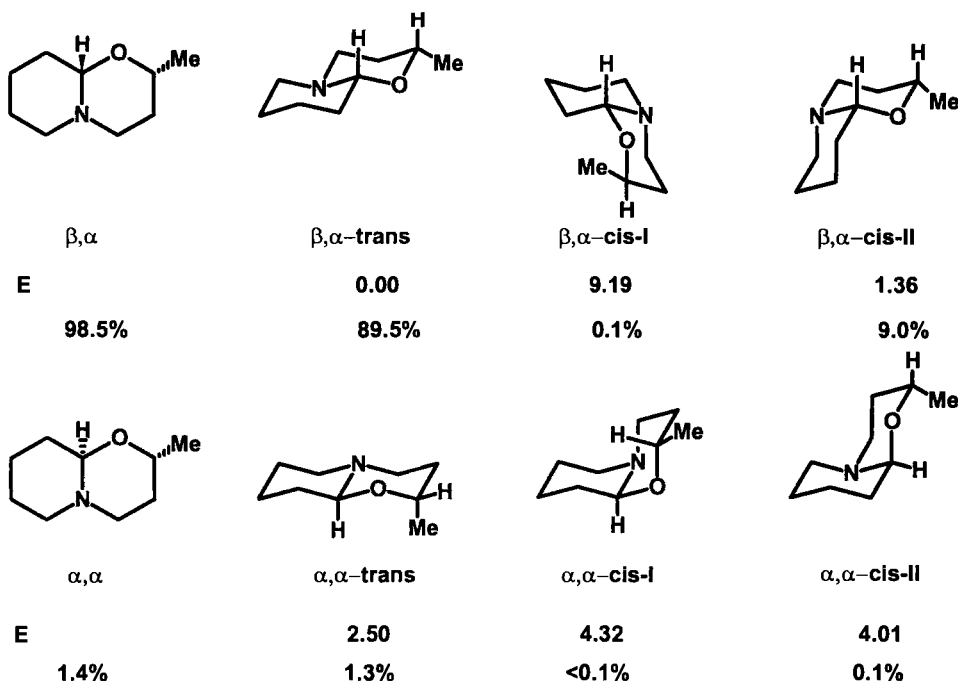


FIG. 1. MM2 energies of 2-methylperhydropyrido[2,1-*b*][1,3]oxazine in chloroform. The top number indicates the energy (kcal · mol<sup>-1</sup>) relative to the most stable species. The bottom numbers indicate the percentage of the Boltzmann equilibrium distribution for all species.

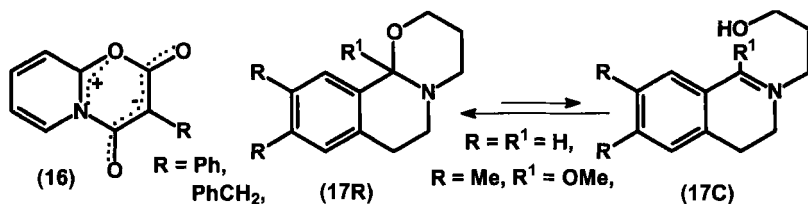
of different conformations of other substituted perhydropyrido[2,1-*b*][1,3]oxazines (92T6325, 92TL507). Bond lengths, bond angles, net atomic charges, HOMO and LUMO energies, dipole moments and the magnetic circular dichroism of mesoionic pyrido[2,1-*b*][1,3]oxazines (**16**) were calculated (85JOC5050; 88CB951).

MM2(91), MMX, and MM2\* molecular mechanics calculations have been performed to determine the relative steric energy of (2*S*)-2-hydroxymethyl-9-methylperhydro[2,1-*b*][1,3]oxazine. MM2(91) calculations predict that the major isomer should be a *cis*-fused conformation, overestimating the influence of anomeric stabilization, but the other calculations give more realistic predictions that the major isomer should be (2*S*)(5*R*)(9*aS*)-*trans* fused (95JOC2989).

### 3. UV Spectroscopy

The UV and magnetic circular dichroism spectra of mesoionic pyrido[2,1-*b*][1,3]oxazine (**16**, R = CH<sub>2</sub>Ph) were measured in acetonitrile (85JOC5050). UV spectra of hexahydro[1,3]oxazino[3,2-*a*]isoquinolines (**17**) indicated that the ring form (**17R**) was present in cyclohexane





(62AP571; 66AP817), and the absorption bands of both tautomers (**17R**) and (**17C**) could be detected in a more polar solvent (water or methanol) in the case of the dimethoxy derivative **17** ( $\text{R} = \text{MeO}$ ,  $\text{R}^1 = \text{Me}$ ) (66AP817). The unsubstituted derivative **17** ( $\text{R} = \text{R}^1 = \text{H}$ ) also existed in the ring form in methanol (62AP571).

#### 4. IR Spectroscopy

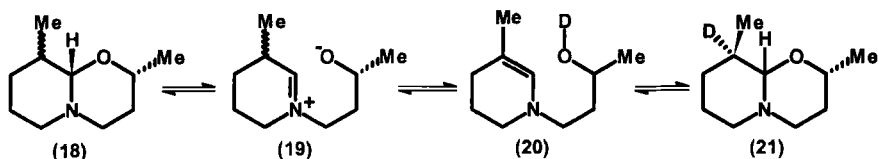
The Bohlmann bands were used to identify the presence of the *trans*-fused conformation of perhydropyrido[2,1-*b*][1,3]oxazines (60JA5148; 84TL3227; 89CPB1676; 92TL507; 96BMC1313) and the heterorings of 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines (61AP645; 66AP817).

#### 5. $^1\text{H}$ NMR Spectroscopy

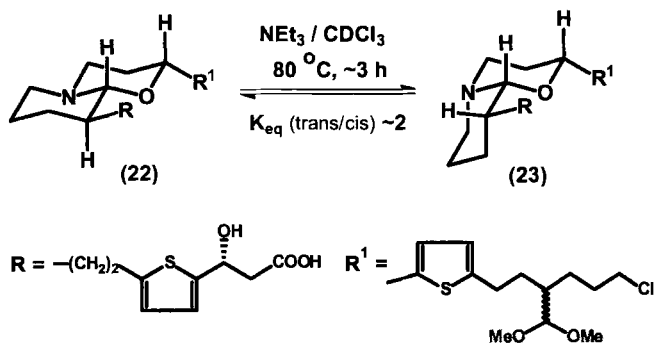
The  $^1\text{H}$  NMR data on perhydropyrido[2,1-*b*][1,3]oxazine suggest there is a rapid equilibrium involving the *trans*-, *cis*-I-, and *cis*-II-fused conformations (see Scheme 4), the predominant contributor to the conformational equilibrium being the *trans*-fused conformer, which is in accordance with the results of quantum chemical calculations (94JOC6904). The coupling constants of 8.5 Hz and 2.5 Hz between 9a-H and 9<sub>ax</sub>-H and 9<sub>eq</sub>-H, respectively, are consistent with the dihedral angles in either the *trans*-fused or the *cis*-I-fused conformation, but not those in the *cis*-II-fused one. The signal of 9a-H is highly shielded ( $\delta$  3.41 ppm), which is consistent with the preference for two sets of nonbonding electrons antiperiplanar to the C-9a-H-9a bond uniquely found in the *trans*-fused conformation. This suggests that the greater degree of anomeric stabilization for the *cis*-II-fused conformer (double) relative to either the *trans*-fused one (single) or the *cis*-I-fused one (single) is energetically insufficient to override the enthalpic destabilization that accompanies the additional axial substituent present in either the *cis*-I-fused or the *cis*-II-fused conformer.

9-Methylperhydropyrido[2,1-*b*][1,3]oxazine and its 9-butyl derivative were prepared as 6:1 and 5:1 mixtures of the  $\beta\beta$ - and  $\beta\alpha$ -diastereomers, respectively (90TL4281; 94JOC6904). These mixtures were not separable by

either liquid or gas chromatography, suggesting that ring opening of the 1,3-oxazine ring is both rapid and reversible (see Scheme 5). The ratio for the equilibrium mixtures of the 2-methyl and 2-butyl derivatives was estimated to be  $\sim 30:1$ , in favor of the equatorially alkylated *trans*-fused conformers (90TL4281; 94JOC6904). It proved possible to separate a 3:1 mixture of the 2,9-dimethyl and 2,9-dibutyl derivatives to the diastereomers by means of HPLC on silica gel. Only two ( $\beta\beta\alpha$  and  $\alpha\beta\alpha$ ) of the four possible diastereomers were observed.



A 3:1 mixture of the diastereomers of 2,9-dimethylperhydropyrido[2,1-*b*][1,3]oxazine (**18**) after standing in  $D_2O$  in the presence of DBr at  $80^\circ C$  for 24 h gave the single species **21** · DBr in which both H-9a and the 9-methyl group yielded singlets. This set of observations is entirely consistent with rapid epimerization of the aminal centers (C-9a) through iminium ions **19**. A slow proton loss from **19** gives the enamine **20**, and subsequent deuteration at either face of the enamine **20** provides a pathway for the isomerization of C-9 relative to C-2, allowing the formation of essentially only the C-9-deuterated **21** (90TL4281). Acidic equilibration of a 1:1 kinetic mixture of diastereomer 2,9-dimethylperhydropyrido[2,1-*b*][1,3]oxazine gave a 30:1 mixture of the *trans*- and *cis*-fused isomers, containing both methyl groups in equatorial positions (92TL507).



The relative configuration of the 2-phenyl group in *trans*-fused *cis*-2,9a-*H*-2(*S*)-phenylperhydropyrido[2,1-*b*][1,3]oxazine was established in NOE experiments (94TL1715). The *cis* isomer **23** could be equilibrated with the *trans* isomer **22** in the presence of triethylamine in CDCl<sub>3</sub> at 80°C (94JA2617).

## 6. <sup>13</sup>C NMR Spectroscopy

The chemical shift for C-9a in the *cis*-fused conformation of perhydropyrido[2,1-*b*][1,3]oxazines indicates that this carbon atom is shielded relative to C-9a in the *trans*-fused conformation (see Table I) (93T4315). Structures of aragupetrosine A and different members of the xestospongine/aragupongine alkaloids containing one or two perhydropyrido[2,1-*b*][1,3]oxazine moieties were characterized by <sup>1</sup>H and <sup>13</sup>C NMR investigations (84TL3227; 89CPB1676; 89TL4149; 92JNP1505; 94JOC6904; 96BMC1313).

TABLE I  
SOME CHARACTERISTIC <sup>1</sup>H AND <sup>13</sup>C NMR DATA FOR PERHYDROPYRIDO[2,1-*b*][1,3]OXAZINES  
IN CDCl<sub>3</sub>

Substituent	Predominant conformer	H-9a		C-9a, ppm	Ref.
		δ ppm	J <sub>9,9a</sub> , Hz		
Unsubstituted	<i>trans</i>	3.41 dd	8.5 and 2.5		90TL4281
2-CH <sub>2</sub> OCH <sub>2</sub> Ph		3.46 dd	8.9 and 1.7	92.35	95JOC2989
2-Me(eq)	<i>trans</i>	3.45 dd	8.9 and 2.9		90TL4281
2-CH <sub>2</sub> OH(eq)	<i>trans</i>	3.48 dd	12 and 3	92.2	92T6325
2-CH <sub>2</sub> OAc		3.46 dd	8.7 and 3	92.44	95JOC2989
2-CH <sub>2</sub> OTBS	<i>trans</i>			92.2	92TL507
2-CH <sub>2</sub> OH,9-(CH <sub>2</sub> ) <sub>5</sub> -OTBDPS	<i>trans</i>	3.08 d	8.3	96.8	95JOC2989
	<i>cis</i>	4.10 br		89.2	95JOC2989
2-Ph(eq)	<i>trans</i>	3.67 dd	8.78 and 2.73	92.60	93T4315
2-Ph(eq),7-Me(eq)	<i>trans</i>	3.49 dd	9.82 and 3.22	93.56	93T4315
	<i>cis</i>	4.47 t	3.27	87.50	93T4315
2-Ph(eq),7-COOEt(eq)	<i>trans</i>	3.60 dd	9.25 and 3.03	92.60	93T4315
	<i>cis</i>	4.39 m		87.53	93T4315
9-Me(eq)	<i>trans</i>	2.80 d	8.4		90TL4281
	<i>cis</i>	3.83 d	2.9		90TL4281
2-Me(eq), 9-Me(eq)	<i>trans</i>	2.95 d	8.2		90TL4281
	<i>cis</i>	3.89 d	2.7		90TL4281

TBDPS, *tert*-butyldiphenylsilyl.

## 7. Mass Spectrometry

The structure of 9*a*-methylperhydropyrido[2,1-*b*][1,3]oxazine-6-one was characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and mass spectroscopy [91JCS(P2)735].

## 8. X-Ray Investigations

The structure of *cis*-5*a*,6-*trans*-9-*H*-6,9-dimethyl-5*a*,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-11-one was confirmed by means of single-crystal X-ray analysis (89TL7321). Both methyl groups occupy pseudoaxial positions, with the piperidine moiety in a chairlike conformation. The crystal unit of (2*S*,5*R*,9*aS*)-*cis*-2,9*a*-*H*-2-hydroxymethylperhydropyrido[2,1-*b*][1,3]oxazine hydrochloride contains two crystallographically independent molecules, adopting *trans*-fused conformations with a differently oriented hydroxy group in the equatorial hydroxymethyl moiety (95JOC2989). The solid-state structures of the xestospongine C (83MI1; 84TL3227) and (±)-xestospongine D (96BMC1313) alkaloids, containing two perhydropyrido[2,1-*b*][1,3]oxazine moieties, were determined by X-ray investigations.

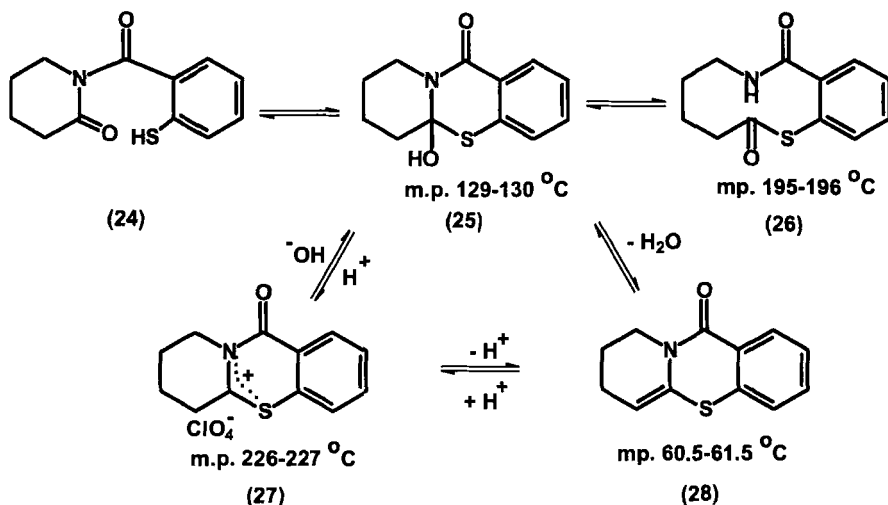
# B. PYRIDO[2,1-*b*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

## 1. Tautomerization

1-(2-Mercaptobenzoyl)-2-piperidinone (**24**) spontaneously isomerizes into the thiacyclol (**25**), which is stable at temperatures below  $-15^\circ\text{C}$  but is slowly converted to the cyclothiodepsipeptide (**26**) in aqueous methanolic sodium hydroxide (68AG909; 70TL649). The equilibrium concentrations of the tautomers **24**–**26** depend on the nature of the solvent (70TL649). The thiacyclol (**25**) can be transformed to the pyrido[2,1-*b*][1,3]benzothiazinium salt (**27**) by treatment with strong acid, or it can be dehydrated to **28** on heating in inert solvents. These processes are reversible (70TL2467).

## 2. UV and CD Spectroscopy

The UV and CD curves of optically active (*S*)-9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium-4-carboxylate were measured in 1 N hydrochloric acid and in 1 N sodium hydroxide solutions (73ACS1059). The CD spectrum in acid solution exhibits positive bands at 212 and 233 nm and negative bands at 257 and 345 nm, and UV maxima were found at 211, 239, and 342 nm. The two latter bands are associated with the aromatic chromophore. In alkaline solution a bathochromic shift occurred, and the



CD spectrum displayed a positive band at 247 nm and a negative band at 360 nm, whereas the corresponding UV maxima were at 247 and 360 nm.

### 3. $^1\text{H}$ NMR Spectroscopy

$^1\text{H}$  NMR and optical rotation measurement demonstrated that deuterium incorporation on the chiral C-4 in 9-hydroxy-6-methyl-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium-4-carboxylate in 0.4 N sodium hydroxide at 40°C occurred without racemization (73ACS1059).

### 4. X-Ray Crystallography

The structures of *anhydro* 9,9-dimethyl-4-hydroxy-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxide (95JOC3795, 95T6651) and 11*b*-isopropyl-2-methoxy-3,4-diphenyl-2,6,7,11*b*-tetrahydro-[1,3]thiazino-[2,3-*a*]isoquinoline [79AX(B)1285] were determined by means of X-ray diffraction analysis.

## III. Reactivity

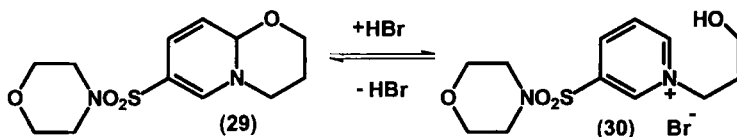
### A. PYRIDO[2,1-*b*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. Ring Opening

The rate of alkaline hydrolysis of 3,4,6,7,8,9-hexahydro-2*H*-pyrido-[2,1-*b*]oxazinium perchlorates to the thermodynamic 1-(3-hydroxypropyl)-

2-piperidones (75CJC2791) decreased with increasing substitution [70JCS(CC)900]. *trans*-6a,10a-*H*-3,4,6,6a,7,8,9,10,10a,11-Decahydro-2*H*-[1,3]oxazino[3,2-*b*]isoquinolinium perchlorate gave 2-(3-hydroxypropyl)perhydroisoquinol-3-one under basic conditions (75CJC2791). Both perchlorates were stable under acidic conditions (75CJC2791, 75CJC3029).

Ring-opened products were obtained from 1,2,3,4,4a,6-hexahydropyrido[1,2-*a*][3,1]benzoxazin-6-ones by alkaline hydrolysis [70KGS879; 89IJC(B)126; 90MI1, 90RRC55; 92MI3], and from 2*H*,11*bH*-[1,3]oxazino[2,3-*a*]isoquinoline-2,2,3,4-tetracarboxylate by acidic hydrolysis or by treatment with aniline (67CB1094). Heating 1-[(trichloroacetyl)imino]-3-trichloromethyl-1*H*-[1,3]oxazino[3,2-*a*]quinoline in water gave trichloroacetamide and quinoline (73IZV456). Solvolysis of 6-benzyloxy-2-phenyl-3-oxo-3*H*-[1,3]oxazino[3,2-*a*]quinolinium-1-olate afforded 4-benzyloxyquinolin-2(1*H*)-one and phenylmalonic acid derivatives (76M859).



Tetrahydropyrido[2,1-*b*][1,3]oxazine (29) afforded pyridinium bromide (30) on the action of aqueous hydrogen bromide, and no reaction occurred on treatment with NaBH<sub>4</sub> in methanol [77JCS(P2)759]. Treatment of 3-oxo-2,3,7,8,9,10-hexahydro-1*H*-[1,3]oxazino[3,2-*a*]quinolinium chloride with ethanol yielded 1-(2-carboxyethyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolinone (69MI1).

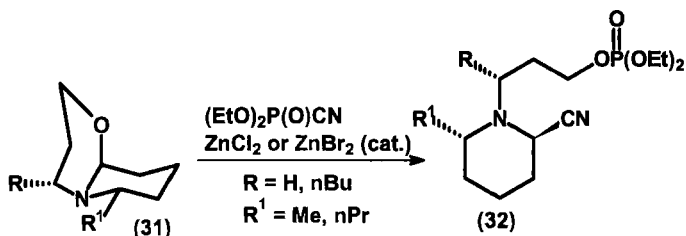
Catalytic reduction of 3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium iodide (60CB61; 61AP65), perhydropyrido[2,1-*b*][1,3]oxazine and its methiodide (61AP65), and 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines (62AP571; 66AP817) over PtO<sub>2</sub>, and reduction of perhydropyrido[2,1-*b*][1,3]oxazine and its 4-oxo derivative with LAH (61AP65), or that of 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines with NaBH<sub>4</sub> in acidified methanol (pH = 4) (67AP308), or with LAH (71MI1) afforded 1-(3-hydroxypropyl)piperidine or its appropriate derivatives.

Oxidation of perhydropyrido[2,1-*b*][1,3]oxazines with Hg(OAc)<sub>2</sub> yielded 1-(3-hydroxypropyl)-2-piperidones (60JA5148; 63AP38). Oxidation of 2-phenyl-2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinoline with the Hg(OAc)<sub>2</sub>-EDTA reagent gave 2-(3-phenyl-3-hydroxypropyl)-1,2,3,4-tetrahydroisoquinolin-1-one (67AP308). Anodic overoxidation of perhydropyrido[2,1-*b*][1,3]oxazin-6-one afforded *N*-(3-hydroxypropyl)glutari-

amide, probably via 9a-hydroxyperhydropyrido[2,1-*b*][1,3]oxazin-6-one [80H(14)1089].

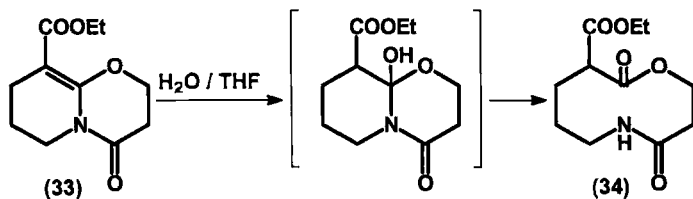
Reaction of 2-ethoxy-3,3-dimethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium chloride with sodium ethylate, trimethylsilyl cyanide, or aqueous sodium bicarbonate yielded ring-opened products (91ZOB2743).

When *cis*-6,9a-*H*-6-alkylperhydropyrido[2,1-*b*][1,3]oxazines reacted with *n*-butylmagnesium bromide in diethyl ether at  $-20^{\circ}\text{C}$ , *cis*-2,6-*H*-1-(3-hydroxypropyl)-2-butyl-6-alkylpiperidines were obtained (91TL5147; 92T8295).



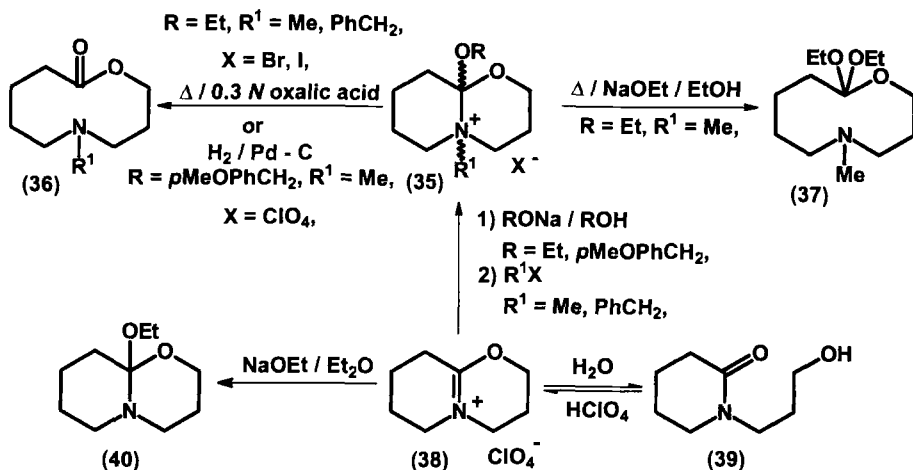
The reaction of *cis*-fused perhydropyrido[2,1-*b*][1,3]oxazines (31) with diethyl cyanophosphonate in the presence of a catalytic amount of  $\text{ZnCl}_2$  or  $\text{ZnBr}_2$  provided 2-cyanopiperidines (32) [88H(27)1575; 91SL44, 91SL878].

Treatment of 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines with hydrogen bromide, benzylmagnesium chloride, acyl chloride, or hydrogen cyanide afforded ring-opened 1,2,3,4-tetrahydroisoquinoline derivatives (66AP817).



Treatment of hexahydropyrido[2,1-*b*]oxazin-4-one (33) with water in THF yielded the monocycle 34 (67ZOB1703). Ten-membered lactones (36) were obtained from 9a-alkoxyperhydropyrido[2,1-*b*][1,3]oxazines (35;  $\text{R} = \text{Et}, p\text{-MeOPhCH}_2$ ;  $\text{R}^1 = \text{Me}, \text{PhCH}_2$ ) (79TL809). Heating 35 ( $\text{R} = \text{Et}, \text{R}^1 = \text{Me}$ ) in ethanolic sodium ethylate yielded the cyclic orthoester (37). 1-(3-Hydroxypropyl)-2-piperidinone (39) was obtained by treatment of 38 with water (79TL809). Ring-opened products formed when 8-(4-

methoxyphenyl)-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazine-2,6-dione reacted with 4-arylpiperazines (93JIC261).



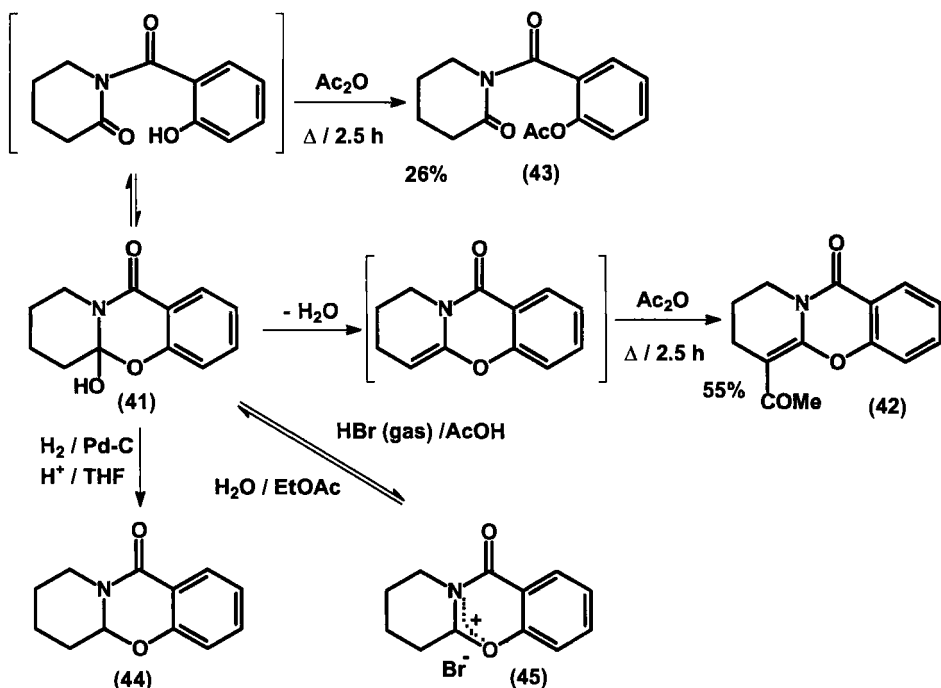
## 2. Reactivity of Rings

Methiodides have been prepared from perhydropyrido[2,1-*b*][1,3]oxazines (61AP65; 63AP38) and 9,10-dimethoxy-2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolines (66AP817; 85AJC1591). In the reaction of perhydropyrido[2,1-*b*][1,3]oxazine and methyl iodide, two methiodides (42%, mp 138–139°C; and 7.5%, mp 224–225°C) were obtained (61AP65).

The bicyclic lactam acetal (**40**) was formed when pyrido[2,1-*b*][1,3]-oxazinium perchlorate (**38**) was treated with sodium methylate [70JCS(CC)900]. Treatment of **38** with sodium alcoholate and then with an alkyl halide gave quaternary salts **35**, presumably as a mixtures of two stereoisomers (79TL809).

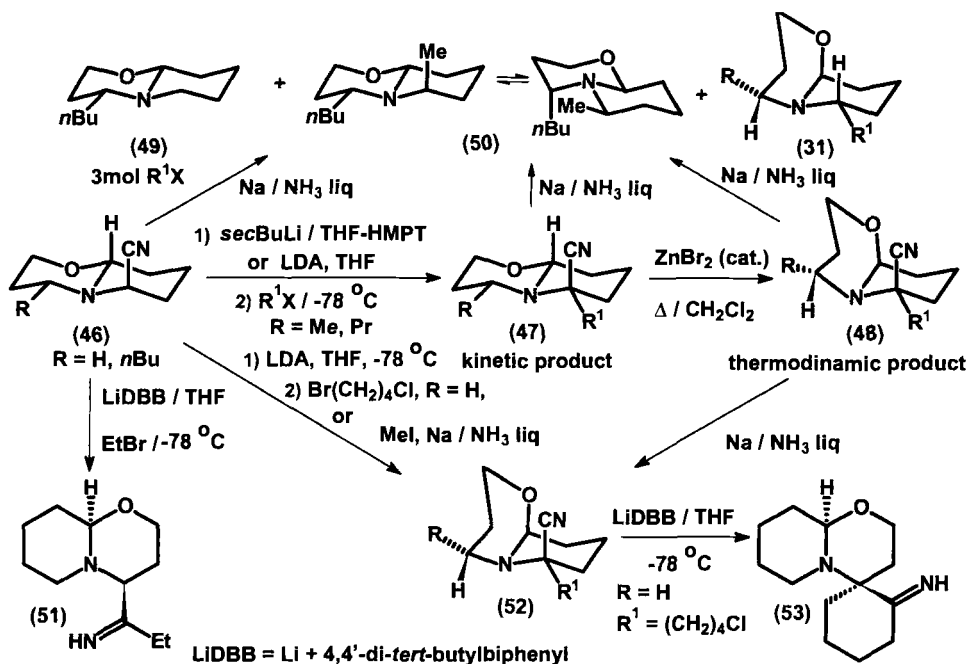
Diazonium coupling of 8-methyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazine-9-carboxamide with aryldiazonium salts in aqueous solution between pH 6 and 7 for 5 h yielded 7-aryazo-8-methyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazinecarboxamides (89EUP316779). Heating 5*a*-hydroxyhexahydropyrido[2,1-*b*][1,3]benzoxazin-11-one (**41**) in acetic anhydride gave a mixture of 6-acetyltetrahydropyrido[2,1-*b*][1,3]-benzoxazin-11-one (**42**) and the ring-opened product **43** (68ZOB2030). Catalytic hydrogenation of the 5*a*-hydroxy derivative (**41**) in acidified THF over Pd/C yielded hexahydropyrido[2,1-*b*][1,3]benzoxazin-11-one (**44**) (65ZOB1389). Treatment of the 5*a*-hydroxy derivative (**41**) with hydrogen bromide in acetic acid afforded the bromide salt (**45**), which could be con-





verted back to the 5*a*-hydroxy derivative (41) with water in ethyl acetate (65ZOB1389).

Treatment of *trans*-fused 6-cyanoperhydropyrido[2,1-*b*][1,3]oxazines (46) with *sec*-BuLi and then with an alkyl halide gave kinetic products 47, which isomerized into the thermodynamic *cis*-fused bicycles 48 under the reaction conditions or on the action of a catalytic amount of  $\text{ZnBr}_2$  [88H(27)1575; 91SL878]. The alkylation was unsuccessful with propyl bromide and tripropyl phosphate under K, THF, and 18-crown-6 conditions (91SL44). Subsequent treatment of 48 or a mixture of 47 and 48 with Na in liquid  $\text{NH}_3$  afforded *cis*-fused pyrido[2,1-*b*][1,3]oxazines (31) with an axial R group. However, a rapid extractive work-up of the reaction mixture of 48 ( $\text{R} = \text{Bu}$ ,  $\text{R}^1 = \text{Me}$ ) gave 31 ( $\text{R} = \text{Bu}$ ,  $\text{R}^1 = \text{Me}$ ) and 50 in a 2:1 ratio (91SL878). When a solution of 46 ( $\text{R} = \text{Bu}$ ) and 3 eq of methyl iodide in THF was added slowly to a solution of sodium in liquid  $\text{NH}_3$ , a complex reaction mixture containing *cis*-4,9*a*-*H*-4-butylperhydropyrido[2,1-*b*][1,3]oxazine (49) and the 4-butyl-6-methylperhydropyrido[2,1-*b*][1,3]oxazines 31 ( $\text{R} = \text{Bu}$ ,  $\text{R}^1 = \text{Me}$ ) and 50 was obtained (91SL878). The reaction of 6-cyanoperhydropyrido[2,1-*b*][1,3]oxazine (46,  $\text{R} = \text{H}$ ) with ethyl bromide in the presence of an organolithium reagent generated *in situ* yielded the



imine **51** (91SL44). Simultaneous addition of propyl bromide and **46** (R = H) to a solution of Na in liq NH<sub>3</sub> decyanated perhydropyrido[2,1-*b*][1,3]oxazine was obtained (91SL44). When **46** (R = H) in THF containing 3 eq of propyl bromide was added dropwise into a stirred solution of Na in liq, NH<sub>3</sub>, alkylated, and decyanated, **31** (R = H, R<sup>1</sup> = Pr) formed (91SL44). Compound **52** [R = H, R<sup>1</sup> = (CH<sub>2</sub>)<sub>4</sub>Cl] with an organolithium reagent gave the *spiro* derivative **53** (91SL44).

Distillation of 6-ethylthioperhydropyrido[2,1-*b*][1,3]oxazine at 155°C gave a small amount of labile 2,3,4,8,9,9a-hexahydropyrido[2,1-*b*][1,3]oxazine (71JOC226).

Reaction of 7-*p*-chlorophenyl-7,8,9,11-tetrahydropyrido[2,1-*b*][1,3]benzoxazin-11-one with hydrazine hydrate yielded the 11-hydrazone derivative [91IJC(B)754].

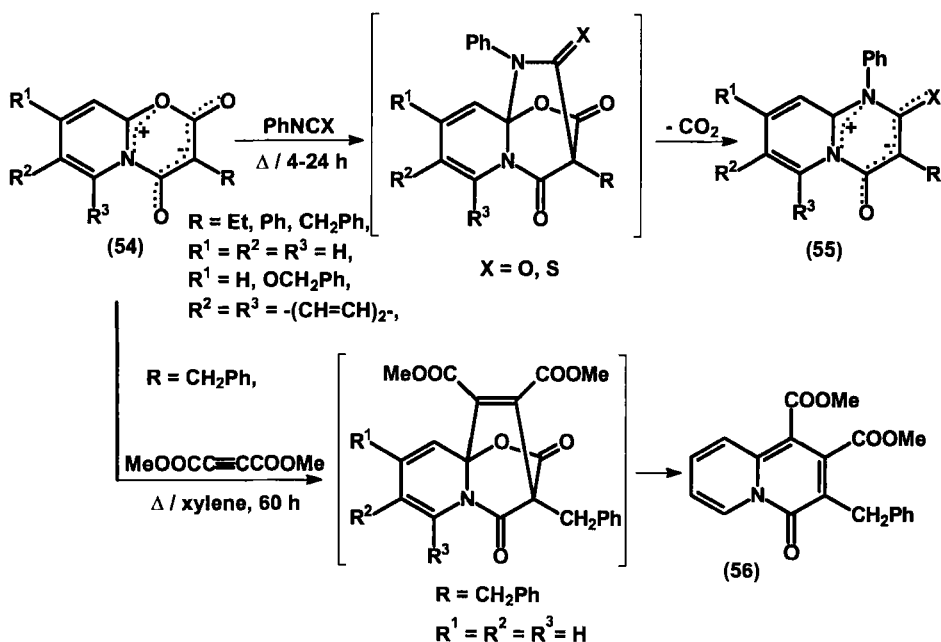
### 3. Reactivity of Substituents Attached to Ring Carbon Atoms

The imino group of the *spiro* derivative (**53**) was hydrolyzed to an oxo group (91SL44). The hydroxy group of 2-hydroxymethylperhydropyrido[2,1-*b*][1,3]oxazines was alkylated and acylated with benzyl bromide in

the presence of sodium hydride in THF and acetic anhydride in the presence of triethylamine, respectively (95JOC2989).

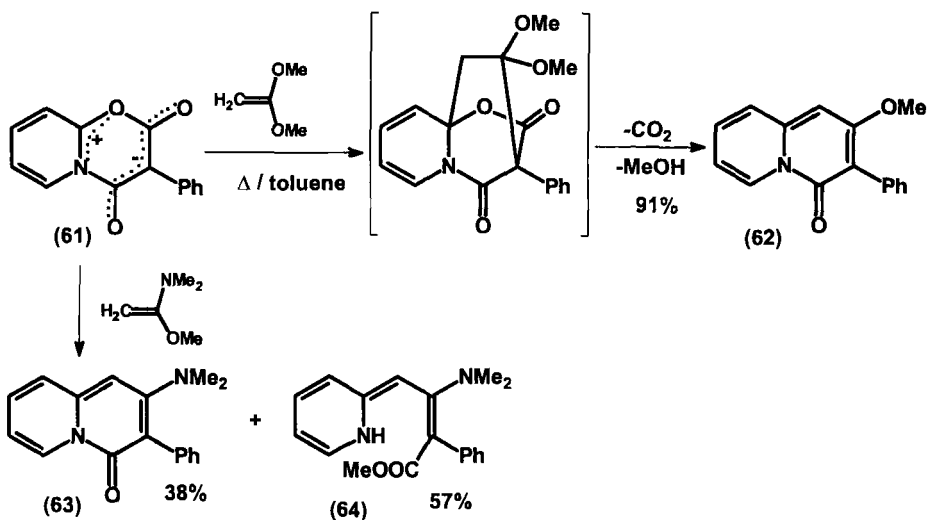
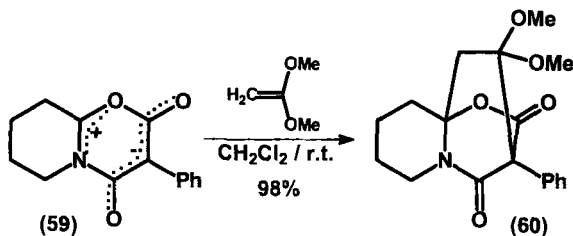
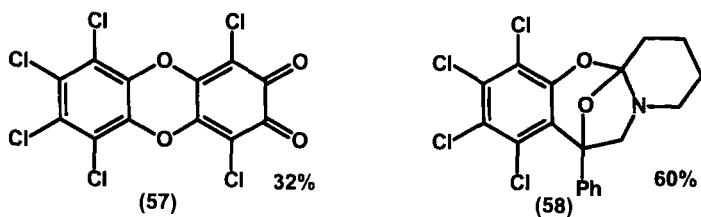
#### 4. Ring Transformation

Treatment of 2-methyl-9a-methoxy-4,6,7,8,9a-hexahydropyrido[2,1-b][1,3]oxazin-4-one with conc. ammonium hydroxide in a sealed tube gave 2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [75H(3)927].



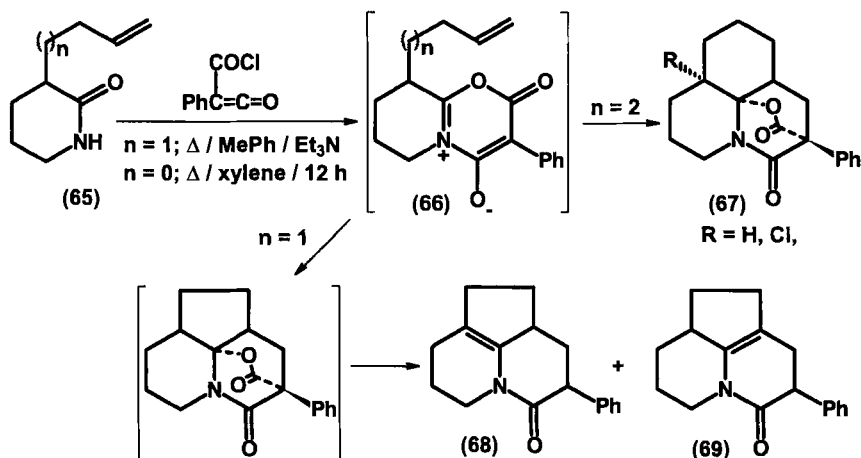
Mesoionic pyrido[2,1-*b*][1,3]oxazines (**54**) afforded 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-iumolates (**55**) and 4*H*-quinolizin-4-one (**56**) with phenyl iso(thio)cyanates [78LA1655; 79CB1585; 82ZN(B)222] and dimethyl acetylenedicarboxylate (79CB1585), respectively. Reaction of 2-cyano-3-methyl-1*H*,6*H*-pyridol[1,2-*a*][3,1]benzoxazine-1,6-dione with ammonium acetate and hydroxylamine, hydrazines, primary aliphatic or aromatic amines, and (thio)ureas gave 5-unsubstituted and 5-substituted 2-cyano-3-methyl-1*H*,6*H*-pyrido[1,2-*a*]quinazoline-1,6-diones (93CCC1953).

From reaction mixtures of tetrachloro-1,2-benzoquinone and **54** ( $\text{R} = \text{CH}_2\text{Ph}$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ) and the 6,7,8,9-tetrahydro derivative of **54** ( $\text{R} = \text{Ph}$ ) in methylene chloride, the tricyclic **57** and tetracyclic **58**, respectively, were isolated [82ZN(B)222].

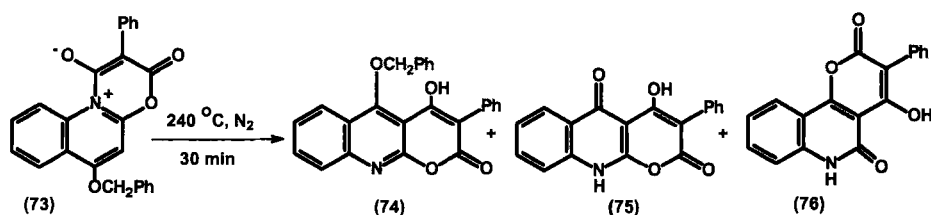
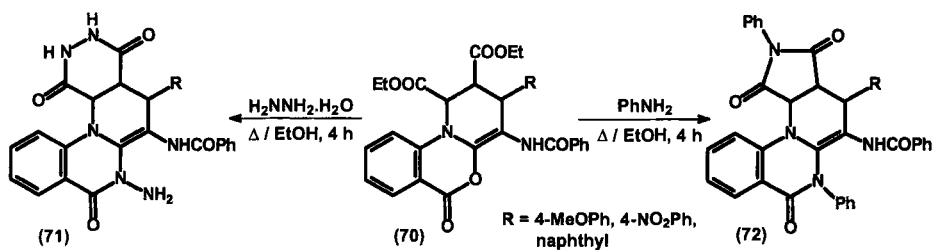


1,4-Dipolar cycloaddition of 1,1-dimethoxyethene to the mesoionic pyrido[2,1-*b*][1,3]oxazoline **59** gave the adduct **60**. The similar reaction with **61** afforded quinazolin-4-one (**62**). When 1-dimethylamino-1-methoxyethylene was applied in the latter reaction, a mixture of quinolizin-4-one (**63**) and the ring-opened product **64** was obtained (88CB951).

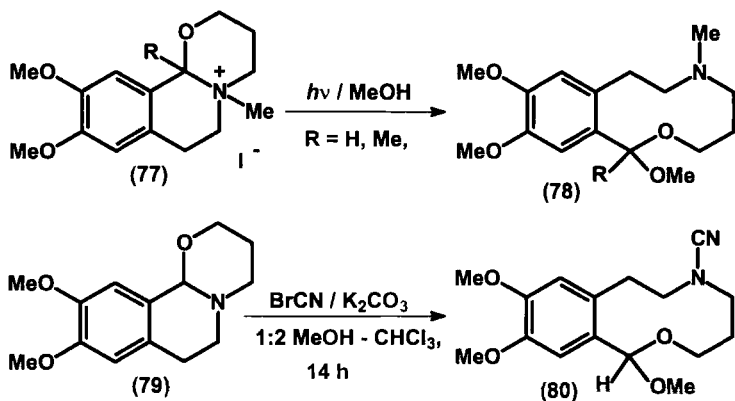
Depending upon the length of the side chain *n*, a cycloadduct (**67**; R = H) and a ring-transformed product (**68**) were obtained via pyrido[2,1-



*b*[[1,3]oxazines (66) in the reaction of piperidones (65) and (chlorocarbonylphenyl) ketene (95JOC3795). Reaction in boiling benzene gave chlorinated 67 ( $R = \text{Cl}$ ) as a by-product and 67 ( $R = \text{H}$ ) from the longer homolog (65,  $n = 2$ ), and a 1:1 isomeric mixture of 68 and 69 was obtained from the lower homolog (65;  $n = 1$ ) at  $110^\circ\text{C}$ .



Reactions of pyrido[1,2-*a*][3,1]benzoxazine-1,2-dicarboxylates (**70**) with hydrazine and aniline afforded the tetracyclic nitrogen bridgehead compounds **71** and **72**, respectively [89IJC(B)126; 90MI1, 90RRC55; 92MI3]. Ring transformation of 1,3-oxazino[3,2-*a*]quinoline (**73**) at 240°C afforded a mixture of **74**, **75**, and **76** in a few percent (76M859).



Photosolvolysis of quaternary iodides **77**, and the reaction of 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*b*]isoquinoline (**79**) with cyanogen bromide afforded 2,6-benzoxazecines **78** and **80**, respectively [79CI(L)319; 80CI(L)421; 85AJC1591; 86AJC893].

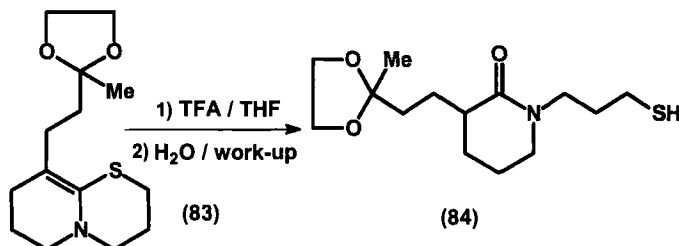
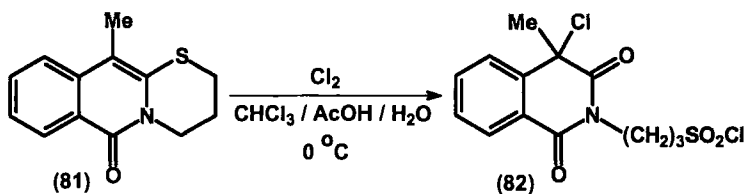
## B. PYRIDO[2,1-*b*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

### 1. Ring Opening

Treatment of **81** with chlorine afforded a ring-opened product (**82**) [80CPB1131, 80JAP(K)80/127372]. A ring-opened product (**84**) was obtained when 9-[3-(2-methyl[1,3]dioxolan-2-yl)ethyl]-2,3,4,6,7,8-hexahydropyrido [2,1-*b*][1,3]thiazine (**83**) was treated with trifluoroacetic acid in boiling THF [94H(37)441].

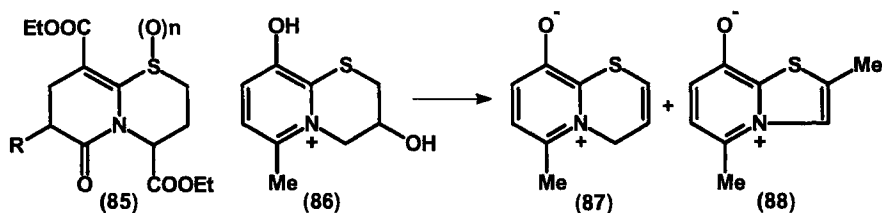
### 2. Reduction

2,3,4,6,7,8-Hexahydropyrido[2,1-*b*][1,3]thiazines were prepared by the reduction of 4-oxo derivatives with LAH [94H(37)441].



### 3. Reactivity of Ring Hetero Atoms

Oxidation of 6-oxopyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylates (**85**;  $n = 0$ ,  $\text{R} = \text{H}$ , phthalamido) with 1 mol eq of 3-chloroperoxybenzoic acid yielded sulfoxides (**85**;  $n = 1$ ,  $\text{R} = \text{H}$ , phthalamido) [83JCS(CC)199; 92JCS(P1)621]. Oxidation of 2,3,4,6,7,11*b*-hexahydro[1,3]thiazino[2,3-*a*]-isoquinolin-4-ones with 3-chloroperoxybenzoic acid in dichloromethane gave sulfones (69FRP1552211). The appropriate sulfone was also prepared from perhydropyrido[2,1-*b*][1,3]thiazine (59AP165) and 3,4,7,8,9,10-hexahydro-2*H*,6*H*-[1,3]thiazino[3,2-*b*]isoquinolin-6-one [79JAP(K)79/92996; 81USP4284778].

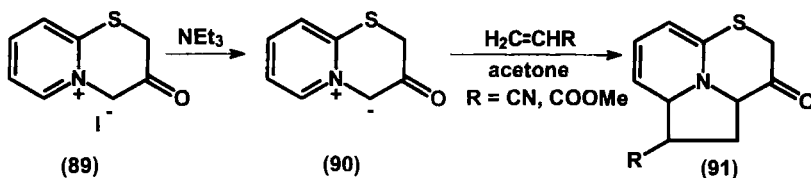


Depending upon the reaction conditions (molar ratio, temperature), oxidation of 4,6-dihydro- and 2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-ones with 30% hydrogen peroxide gave either sulfoxides or sulfones (78BEP866987, 78GEP2756067; 79CPB2372, 79YZ993). Similarly, sulfone

and sulfoxide derivatives were prepared from 4,6-dihydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one with hydrogen peroxide. The yield of sulfone was higher when the oxidation was carried out in dioxane in the presence of a tungsten catalyst at 85–90°C for 2 h (80CPB1131). Perhydropyrido[2,1-*b*][1,3]thiazine-2,2-dioxide was obtained from perhydropyrido[2,1-*b*][1,3]-thiazine with hydrogen peroxide (59AP165).

#### 4. Reactivity of Ring Carbon Atoms

Treatment of 3,6-dihydroxy-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3] thiazinium salt (**86**) with orthophosphoric acid at 140°C for 34 h or with conc. sulfuric acid at ambient temperature for 5 h afforded 1:1 and 3:1 mixtures of pyrido[2,1-*b*][1,3]thiazine (**87**) and thiazolo[3,2-*a*]pyridine (**88**), respectively (70ACS2949). Under basic conditions, only extensive destruction of **86** was observed. When 3-hydroxy-2,3,4,6-tetrahydro[1,3]thiazino[2,3-*a*]isoquinolin-6-one was left to stand in conc. sulfuric acid at room temperature overnight, 4,6-dihydro[1,3]thiazino[2,3-*a*]isoquinolin-6-one was obtained in 61% yield (72ACS1620). 9-Oxido-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium betaine did not undergo cycloaddition even under extreme conditions [81JCR(S)208].



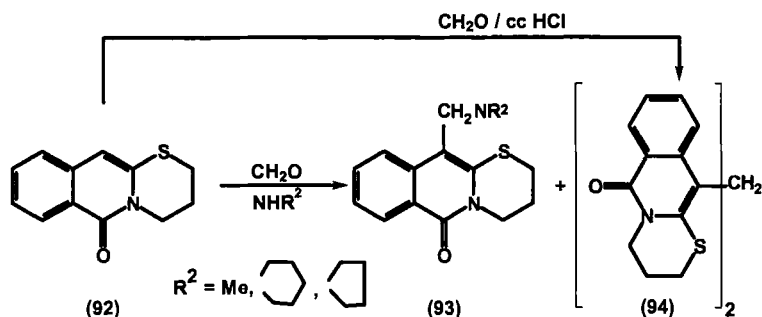
Cycloaddition of ylide **90**, formed from 3-oxopyrido[2,1-*b*][1,3]thiazinium iodide (**89**) on the action of triethylamine, with acrylonitrile or methyl acrylate gave [1,3]thiazino[4,3,2-*cd*]indolizines (**91**), which were subsequently aromatized by treatment with chloranil (80CL947).

4-Phenyl-2,3,4,6,7,11*b*-hexahydro[1,3]thiazino[2,3-*a*]isoquinoline was obtained by the reduction of 4-phenyl-2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium perchlorate and its 3,4-dihydro derivatives with  $\text{KBH}_4$  in methanol (74IJC1242). Reduction of 4-methyl-5,6-dihydro-2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium perchlorate with either  $\text{NaBH}_4$  or sodium cyanoborohydride gave a mixture of 4-methyl-2,3,4,6,7,11*b*-hexahydro[1,3]thiazino[2,3-*a*]isoquinoline and 1,2,3,4-tetrahydroisoquinoline [81IJC(B)372].

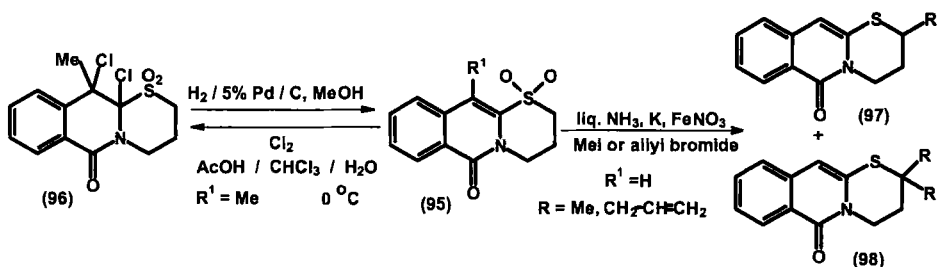
Treatment of 2-(*tert*-butylthio)-11*b*-benzyl-3,4-diphenyl-2,6,7,11*b*-tetrahydro[1,3]thiazino[2,3-*a*]isoquinoline with trityl tetrafluoroborate in acetic anhydride at 0°C gave 11*b*-benzyl-3,4-diphenyl-6,7-dihydro-



11*b*H-[1,3]thiazino[2,3-*a*]isoquinolinium tetrafluoroborate (86S899). 2-Methoxy-11*b*-methyl-3,4-diphenyl-2,6,7,11*b*-tetrahydro[1,3]thiazino[2,3-*a*]isoquinoline was obtained from the 2-ethoxy derivative in methanol containing conc. sulfuric acid (86S899).

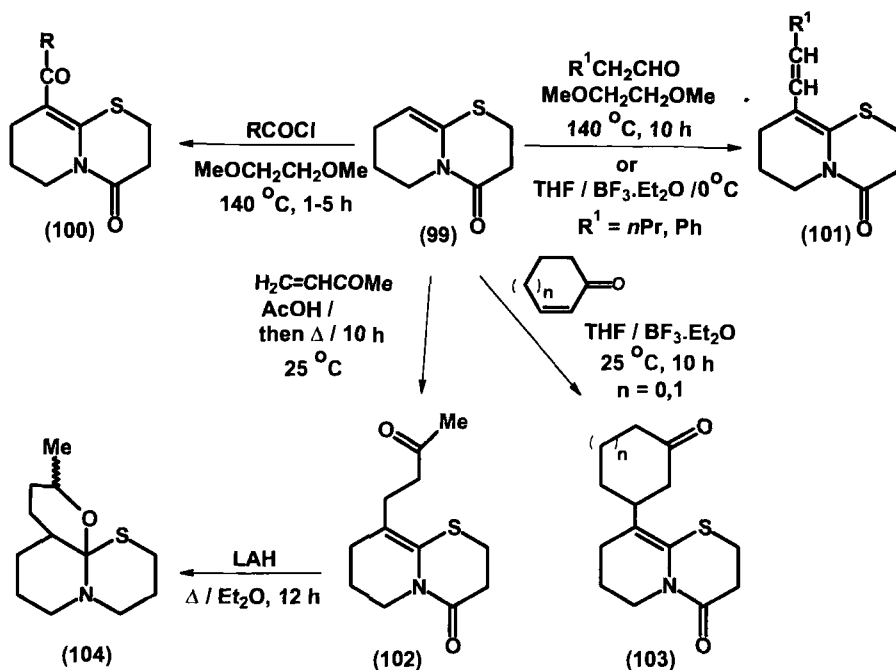


Vielsmeyer-Haack formylation of 2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one (92) gave the 11-formyl derivative, whereas the Mannich reaction afforded 11-aminomethyl derivatives (93) accompanied by an 11,11'-methylene bis product (94) (78BEP866987, 78GEP2756067; 79YZ993). Compound 94 could be obtained in higher yield with formaldehyde in conc. hydrochloric acid (79YZ993). A Pummerer reaction of 2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one sulfoxide yielded the 2-acetoxy derivative of 92 (78BEP866987, 78GEP2756067; 79YZ993). Reaction of 2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one sulfone (95;  $\text{R}^1 = \text{H}$ ) with  $\text{Br}_2$  in acetic acid gave the 11-bromo compound (95;  $\text{R}^1 = \text{Br}$ ) (78BEP866987, 78GEP2756067).



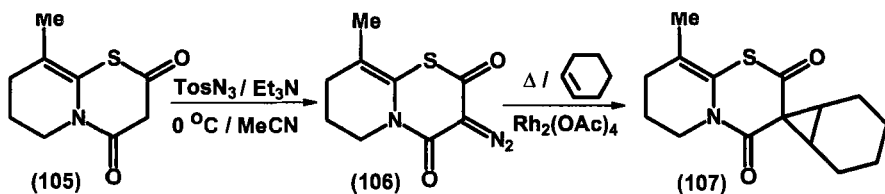
Treatment of sulfone 95 ( $\text{R}^1 = \text{Me}$ ) with  $\text{Cl}_2$  afforded the 11,11*a*-dichloro derivative 96, which could be converted to the starting sulfone (95;  $\text{R}^1 = \text{Me}$ ) by hydrogenation over 5% Pd/C in methanol (80CPB1131). Treatment of 95 ( $\text{R}^1 = \text{H}$ ) in liquid  $\text{NH}_3$  with K in the presence of  $\text{Fe(NO}_3)_3$  and then

with an alkyl halide afforded a mixture of 2-alkyl (**97**) and 2,2-dialkyl (**98**) derivatives [78BEP866987, 78GEP2756067; 79JAP(K)79/92997, 79YZ993], whereas nitration with nitric acid at 6°C afforded an 8-nitro derivative (78BEP866987, 78GEP2756067). Treatment of 2-hydroxy-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one with conc. sulfuric acid gave 4,6-dihydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one (78BEP866987, 78GEP2756067; 79YZ993).



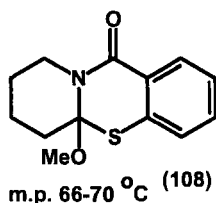
2,3,4,6,7,8-Hexahydropyrido[2,1-*b*][1,3]thiazin-4-one (**99**) was alkylated in the 9-position [94H(37)441]. 2,3,4,6,7,8-Hexahydropyrido[2,1-*b*][1,3]thiazin-4-one (**99**) reacted smoothly with acyl chlorides, aldehydes and  $\alpha,\beta$ -unsaturated ketones to yield 9-substituted derivatives (**100–103**) [94H(37)441]. Reduction of 9-(3-oxobutyl)-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one (**102**) with LAH gave a 1:1 diastereomeric mixture of tricyclic compounds (**104**) [94H(37)441].

Reaction of pyrido[2,1-*b*][1,3]thiazine-2,4-dione (**105**) with *p*-tosyl azide in the presence of triethylamine in acetonitrile at  $0^\circ\text{C}$  gave a 3-diazo derivative (**106**), which reacted with cyclohexene in the presence of a catalytic amount of rhodium acetate under reflux to yield a *spiro* derivative (**107**) [94H(39)219; 95H(41)1631].



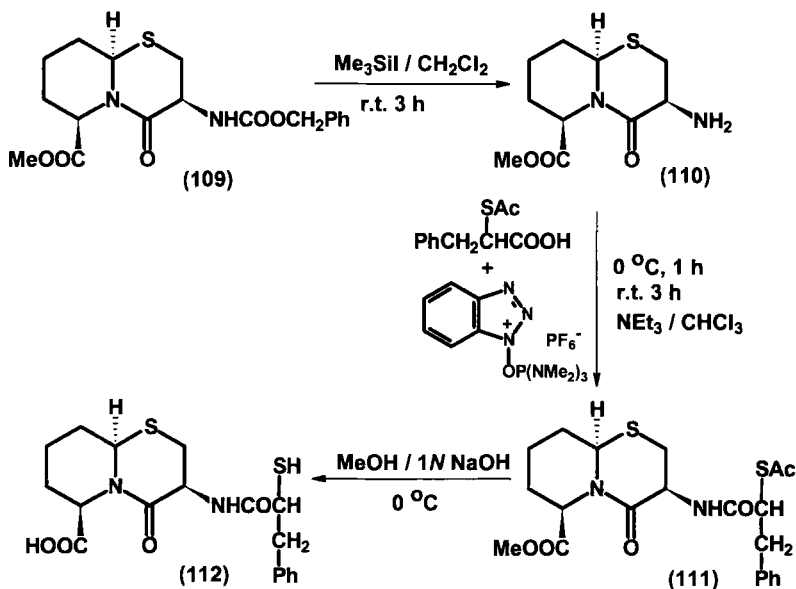
5*a*-Hydroxy- (**25**), 5*a*-methoxyhexahydro- (**108**), and tetrahydro[1,3]-thiazino[3,2-*b*]isoquinolin-11-one (**28**) could be converted to the 11-oxo-6,7,8,9-tetrahydro-11*H*-[1,3]thiazino[3,2-*b*]isoquinolinium salt (**27**) in strong acid. These reactions are reversible. The tetrahydro derivative **28** was prepared from the 5*a*-hydroxy (**25**) and 5*a*-methoxy (**108**) derivatives by elimination of water and methanol, respectively, and from **27** by deprotonation. 5*a*,6,7,8,9,11-Hexahydro[1,3]thiazino[3,2-*b*]isoquinolin-11-one was obtained from the [1,3]thiazino[3,2-*b*]isoquinolinium salt (**27**) by catalytic hydrogenation over Pd/C (70TL2467).

### 5. Reactivity of Substituents Attached to Ring Carbon Atoms



Treatment of 9-(6-trimethylsilylhex-4-enyl)-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one with trifluoroacetic acid yielded the 9-(hex-5-enyl) derivative [94H(37)441]. 9-[3-(2-Methyl[1,3]dioxolan-2-yl)ethyl]-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one was prepared from the corresponding 9-(3-oxobutyl) derivative [94H(37)441]. Prolonged reflux of 6-imino-8-(4-bromophenyl)-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]thiazine-7-carbonitrile in 22% hydrochloric acid afforded only the hydrochloride salt instead of the hydrolysis of the 6-imino group (96JHC1791). Treatment of 11-formyl-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one with sodium borohydride in methanol gave the 11-hydroxymethyl derivative (78BEP866987, 78GEP2756067; 79YZ993), which was reduced catalytically over 5% Pd/C in acetic acid to the 11-methyl derivative (79YZ993). The 2-hydroxy derivative was obtained from 2-acetoxy-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one by treatment with 1 N sodium hydroxide in methanol at room temperature

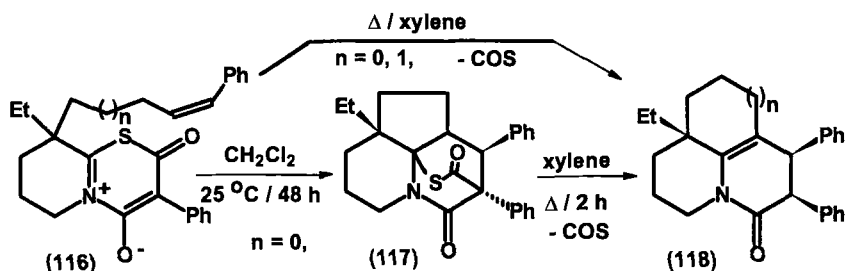
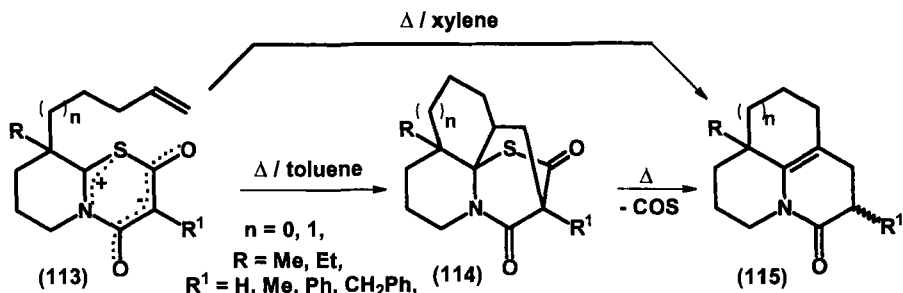
(78BEP866987, 78GEP2756067; 79YZ993). 8-Amino-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one was obtained by catalytic hydrogenation of the 8-nitro derivative over 5% Pd/C in chloroform (78BEP866987, 78GEP2756067). When 9-hydroxy-3,4-dihydro-2H-pyrido[2,1-*b*][1,3]thiazinium bromide in water was passed through a column of Amberlite IRA-401, 3,4-dihydro-2H-pyrido[2,1-*b*][1,3]thiazinium-9-olate was obtained [81JCR(S)208].



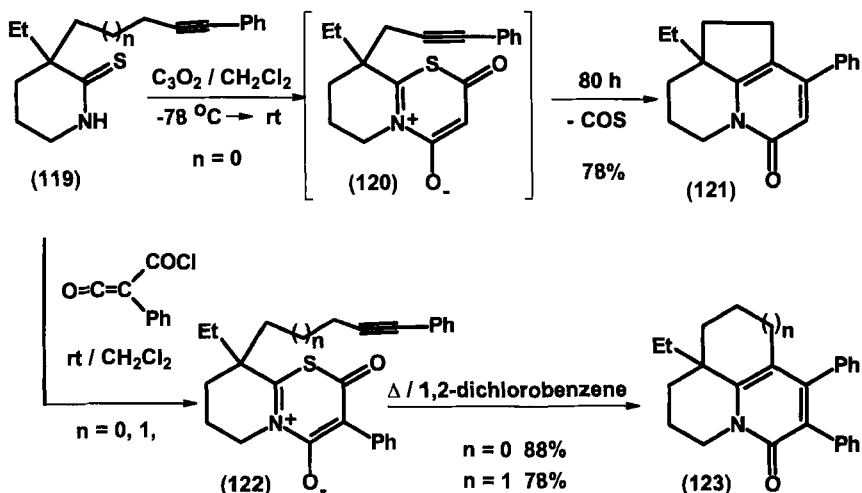
Treatment of 3-acylaminoperhydropyrido[2,1-*b*][1,3]thiazine-6-carboxylate (**109**) with iodotrimethylsilane gave a 3-amino derivative (**110**). The amino group was acylated with (*S*)-2-(acetylthio)-3-phenylpropionic acid in the presence of benzotriazol-1-yloxitris(dimethylamino)phosphonium hexafluorophosphate and triethylamine in dichloromethane, and the product (**111**) was hydrolyzed to **112** (94EUP629627; 96USP5508272).

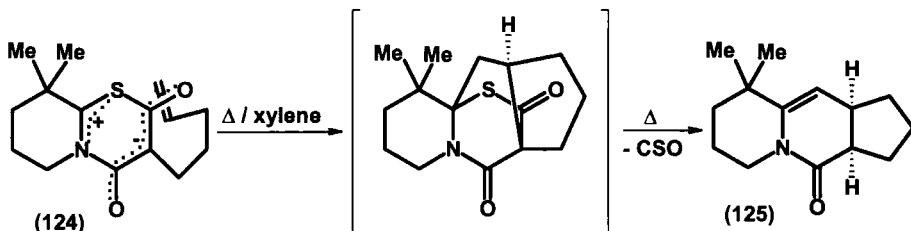
## 6. Ring Transformation

1,4-Dipolar cycloaddition of betaines **113** gave cycloadducts **114**, which produced tricyclic compounds **115** on further thermolysis [93JOC5040; 94H(39)219; 95H(41)1631]. Heating 9,9-disubstituted *anhydro* 4-hydroxy-2-oxo-2H-pyrido[2,1-*b*][1,3]thiazinium hydroxides (**116**) in xylene afforded tricyclic compounds (**118**) as diastereomeric mixtures (95S973). In the case of the lower homolog ( $n = 0$ ) a cycloadduct (**117**) could be also isolated at lower temperature. Reaction of 3,3-disubstituted 2-piperidonethione (**119**;



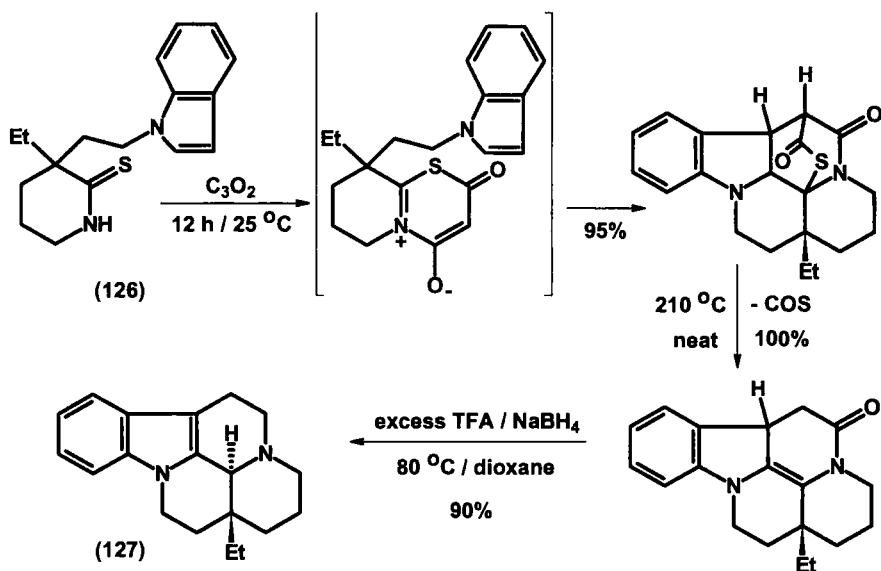
$n = 0$ ) and carbon suboxide afforded tricyclic **121** via a pyrido[2,1-*b*]-[1,3]thiazinium derivative (**120**) (95S973). Heating **122** in 1,2-dichlorobenzene yielded diphenyl derivatives (**123**) (95S973). Similar reaction of pyrido[2,1-*b*][1,3]thiazine (**124**) afforded **125** (93JOC5040; 95JOC3795).



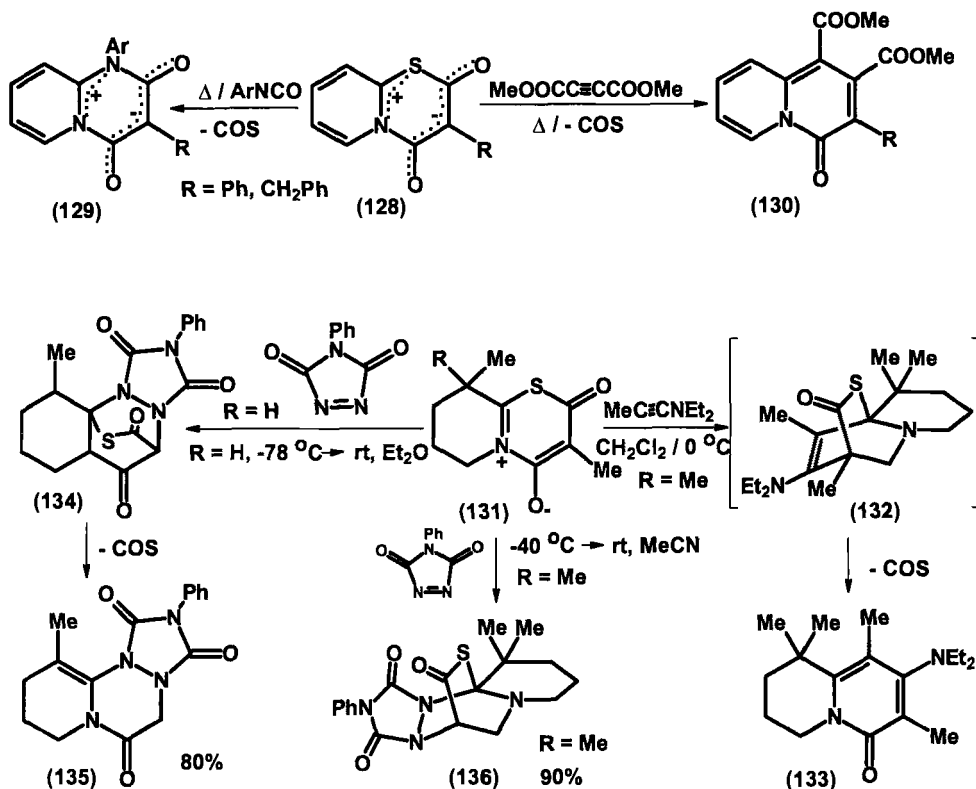


epi-16,17-Dihydroeburnamenine (**127**) was prepared starting from 3-ethyl-3-[2-(1-indolyl)ethyl]-2-piperidinedithione (**126**) and carbon suboxide as depicted in Scheme 6 (96TL335).

1,4-Dipolar cycloaddition of *anhydro* pyrido[2,1-*b*][1,3]thiazinium hydroxides (**128**) with aryl isocyanates and dimethyl acetylenedicarboxylate gave pyrido[1,2]pyrimidines (**129**) and quinolizine-1,2-dicarboxylates (**130**), respectively (76CB3668). 1,4-Dipolar cycloaddition of pyrido[2,1-*b*][1,3]thiazinium betaine (**131**, R = Me) with 1-diethylamino-1-propyne afforded cycloadduct **132**, from which quinolizin-4-one **133** formed by a rapid cheletropic extrusion of carbonyl sulfide (93TL5405; 95T6651). 1,4-Dipolar cycloaddition of *anhydro* 4-hydroxyl-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxides (**131**) and 4-phenyl-1,2,4-triazoline-3,5-dione yielded **135** via **134** [94H(39)219; 95H(41)1631] and **136** (95T6651).



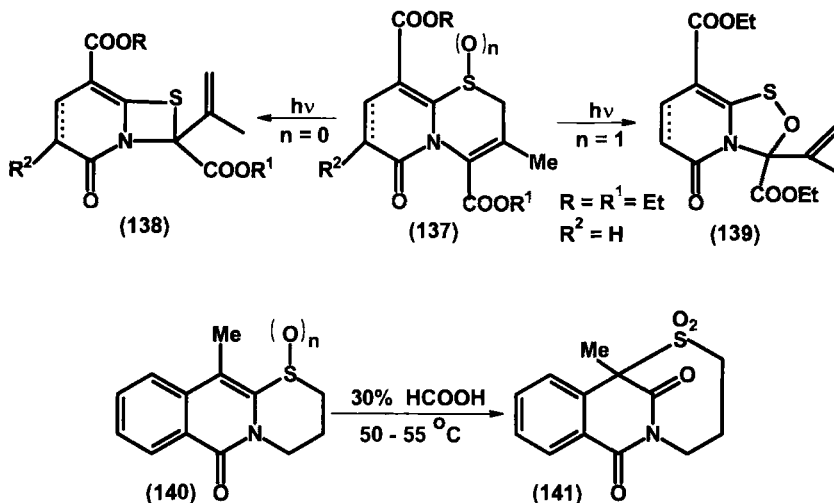
SCHEME 6



Stirring a chloroform solution of 9*a*-amino-2-*tert*-butyl-4,6,7,8,9*a*-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one at 35°C for 64 h afforded 2-*tert*-butyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in 95% yield [89JCS(P1)1231].

Photochemical rearrangement of pyrido[2,1-*b*][1,3]thiazin-6-ones (**137**,  $n = 0$ ) and their sulfoxide derivatives (**137**;  $n = 1$ ) gave thiazetidines (**138**) and 2,1,4-oxathiazolidines (**139**), respectively [82JCS(CC)418; 83JCS(CC)-199; 92JCS(P1)621].

Treatment of 11-methyl-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one (**140**;  $n = 0$ ) and its 1,1-dioxide derivative (**140**;  $n = 2$ ) with excess 30% hydrogen peroxide in 85% formic acid afforded 1,6-methanobenzo[*g*][1,5]thiazonine-7,12-dione (**141**) in 50 and 60% yield, respectively [80CPB1131, 80JAP(K)80/124767]. No cyclization occurred when 9-(pent-4-enyl)-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazine and its 4-oxo derivative was treated with a Lewis acid [94H(37)441].



## IV. Synthesis

### A. PYRIDO[2,1-*b*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

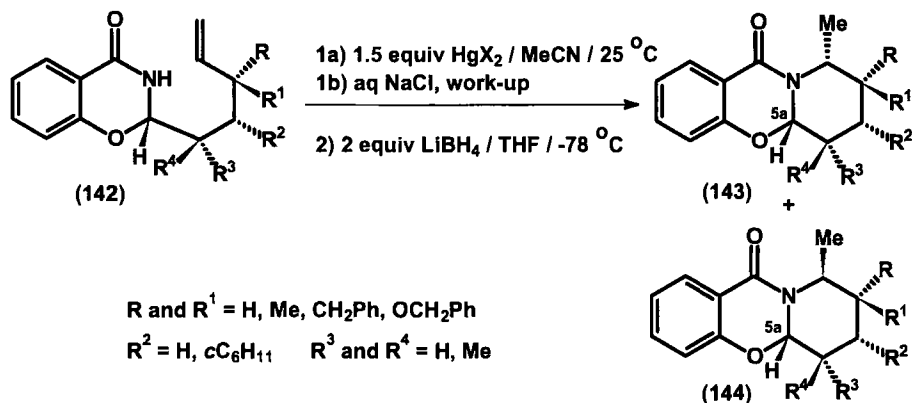
#### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )]

Electrophilic heterocyclizations of 2-(pent-1-en-5-yl)-1,3-benzoxazin-4-ones (**142**) and their C-2 epimers afforded diastereomeric mixtures of 9-methyl-5a,6,7,8,9,11-hexahydropyrido[2,1-*b*][1,3]benzoxazin-10-ones (**143** and **144**), and their C-5a epimers, respectively, containing the 9-methyl group in the pseudo-axial orientation (89TL7321; 90TL6765). Diastereomers **143** and **144** interconvert in response to acidic catalysis (89TL7321).

#### 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )]

Perhydropyrido[2,1-*b*][1,3]oxazines and their 6-oxo derivatives [79MI1; 80H(14)1089] were prepared, sometimes as diastereomeric mixtures, from the corresponding 1-(3-hydroxypropyl)piperidine or its 6-oxo derivative by oxidation with Hg(OAc)<sub>2</sub> in 5% acetic acid (60JA5148; 61AP65; 63AP38; 93T4315), with alkaline K<sub>3</sub>Fe(CN)<sub>6</sub> in 2 M potassium hydroxide [71JCS (B)1745], with ClO<sub>2</sub> in basic medium (optimum pH 9–11) (88JA4829), by anodic oxidation [79MI1; 80H(14)1089], or by photolysis in acetonitrile in the presence of methyl viologen and 1,4-dicyanonaphthalene (DCN) as





an electron acceptor (88TL4153; 91TL5147; 92T8295), or in the presence of 20 eq of acetone (94TL1715). When the reaction period was relatively long or the sodium salt of EDTA was present in the case of  $\text{Hg}(\text{OAc})_2$ , 1-(3-hydroxypropyl)-2-piperidones accompanied the bicyclic products (60JA5148; 61AP65; 63AP38) or were the sole products (60JA5148; 79TL809). Oxidation of 1-(3-hydroxypropyl)-3,5-dimethylpiperidine with  $\text{Hg}(\text{OAc})_2$  gave solely 1-(3-hydroxypropyl)-3,5-dimethyl-2-piperidone (60JA5148). 2-Phenyl-2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinoline was an intermediate when *N*-(3-hydroxy-3-phenylpropyl)-1,2,3,4,-tetrahydroisoquinoline was oxidized with the  $\text{Hg}(\text{OAc})_2$ -EDTA reagent to *N*-(3-hydroxy-3-phenylpropyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline (67AP308). Oxidation of (*S*)-1-(3-phenyl-3-hydroxypropyl)piperidine and its 3-substituted derivatives with  $\text{Hg}(\text{OAc})_2$  in acetic acid gave (*S*)-2-phenylperhydropyrido[2,1-*b*][1,3]oxazine and diastereomeric mixtures of its 7-substituted derivatives (93T4315). Photooxidation of 1-(3-phenyl-3-hydroxypropyl)piperidine in acetonitrile in the presence of 20 eq of acetone led exclusively to *cis*-2,9*a*-*H*-2-phenylperhydropyrido[2,1-*b*][1,3]oxazine (94TL1715).

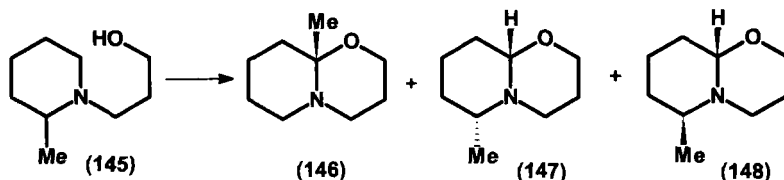
In the case of  $\text{Hg}(\text{OAc})_2$  (60JA5148), ring closure at the more substituted  $\alpha$ -carbon of an unsymmetrical tertiary amine (e.g., **146**) predominated (see Table II), whereas oxidation with  $\text{ClO}_2$  (88JA4829) favored formation of the less substituted products as a 3:1 mixture of two epimers, **147** and **148**, and the photoinduced electron transfer-initiated cyclization of **145** gave only 6-methylperhydropyrido[2,1-*b*][1,3]oxazine as a 24:1 mixture of the two epimers **147** and **148** (91TL5147; 92T8295), or as a 3:1 mixture of **147** and **148** (94TL1715). Oxidation of 1-(3-hydroxypropyl)-2,6-dimethylpiperidine with  $\text{Hg}(\text{OAc})_2$  at  $76^\circ\text{C}$  yielded 6,9*a*-dimethylperhydropyrido[2,1-*b*][1,3]oxazine, as a *ca.* 24:1 mixture of two stereoisomers (60JA5148).

TABLE II  
CONDITIONS AND RESULTS OF THE OXIDATIVE CYCLIZATIONS OF 1-(3-HYDROXYPROPYL)-2-METHYLPYRIDINE (**145**)

Reagent	Medium	Temp.	Relative amounts		Total yield	Ref.
			( <b>146</b> )	( <b>147</b> ) + ( <b>148</b> )		
Hg(OAc) <sub>2</sub>	5% acetic acid	95°C	9	1	57%	60JA5148
		60–65°C	9	1	56%	88JA4829
ClO <sub>2</sub>	basic (pH ≈ 9)	0–5°C	2	9 + 3	48%	60JA5148
Photolysis	MeCN <sup>a</sup>	r.t.	—	24 + 1	92%	88JA4829
				16 + 1	92%	92T8295
Photolysis	MeCN <sup>b</sup>	r.t.	—	3 + 1	48%	91TL5147
				3 + 1	48%	94TL1715

<sup>a</sup> In the presence of 1,4-dicyanonaphthalene and methyl viologen (MW<sup>++</sup>).

<sup>b</sup> In the presence of 20 eq of acetone.

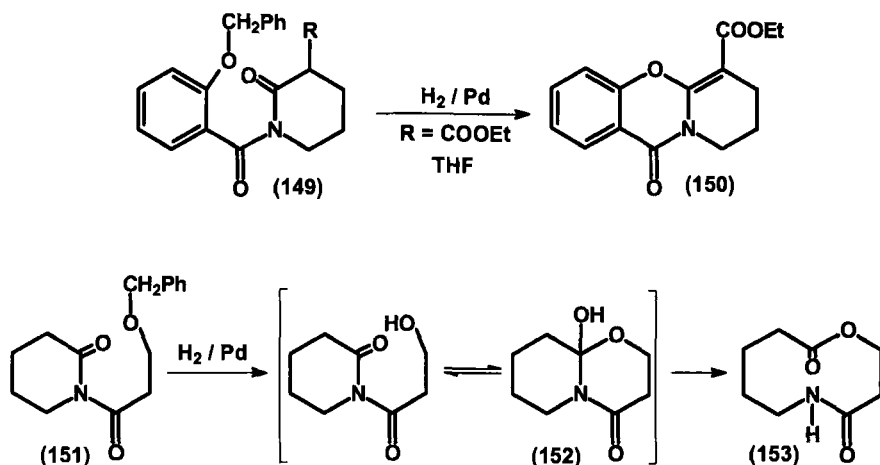


When *o*-(1-piperidyl)benzyl alcohol was stirred in methylene chloride in the presence of an excess of active MnO<sub>2</sub>, a 9:1 mixture of 1,2,3,4,4*a*,6-hexahydropyrido[1,2-*a*][3,1]benzoxazine and *o*-(1-piperidyl)benzaldehyde was obtained (83TL2213). 1,2,3,4,4*a*,6-Hexahydropyrido[1,2-*a*][3,1]benzoxazin-6-ones were prepared from *o*-(2-piperidyl)benzoic acids either with MnO<sub>2</sub> in chloroform [68JCS(C)1722], or with the Hg(OAc)<sub>2</sub>-EDTA reagent (81AP524; 82AP119).

A 7-substituted 3,4,6,7-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]oxazine was formed as by-product the alkylation of methyl 2-(benzyloxycarbonyl-6-oxo-1-phenylsulfonyl)indol-2-yl)-2-azabicyclo[2,2,2]octane-6-*endo*-carboxylate with 3-iodopropanol from a 3-substituted 1-(3-hydroxypropyl)-2,3-dihydropyridinium intermediate (90JOC6028).

Thermal isomerization of 1-trifluoroacetyl-2-(1-piperidyl)benzenes or their hydrates by heating in 1-butanol for 20–90 h gave diastereomeric mixtures of 6-trifluoromethyl-1,2,3,4,4*a*,6-hexahydropyrido[1,2-*a*][3,1]benzoxazines (83TL3923; 89RTC147). Cyclization did not occur under acidic conditions (88TL4599).

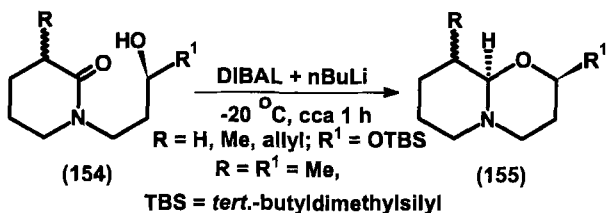
Hydrogenolysis of the piperidone derivative **149** over Pd afforded the tetrahydro carboxylate **150** when R was COOEt, but when R was H, the



product was **41** (65ZOB1389; 68ZOB2030). When the hydrogenolysis of **149** ( $R = \text{H}$ ) was carried out in acidified THF, hexahydropyrido[2,1-*b*][1,3]benzoxazin-11-one (**44**) was obtained (65ZOB1389). The similar reaction of piperidone **151** yielded **153** via 9*a*-hydroxyperhydropyrido[2,1-*b*][1,3]oxazine (**152**) (65ZOB1389).

On treatment of 1-(3-hydroxypropyl)-3-morpholin sulphonylpyridinium bromide (**30**) with potassium *tert*-butoxide in acetonitrile, 7-morpholin sulfonyl-2,3,4,9*a*-tetrahydropyrido[2,1-*b*][1,3]oxazine (**29**) was formed [77JCS-(P2)759].

Irradiation of 4,6-dimethyl-1-(3-hydroxypropyl)-2(1*H*)-pyridone in methylene chloride in the presence of methylene blue as a sensitizer and of *p*-toluenesulfonic acid as a catalyst under an oxygen atmosphere afforded 8,9*a*-dimethyl-2,3,4,6,7,9*a*-hexahydropyrido[2,1-*b*][1,3]oxazine-6,7-dione (87CPB507).



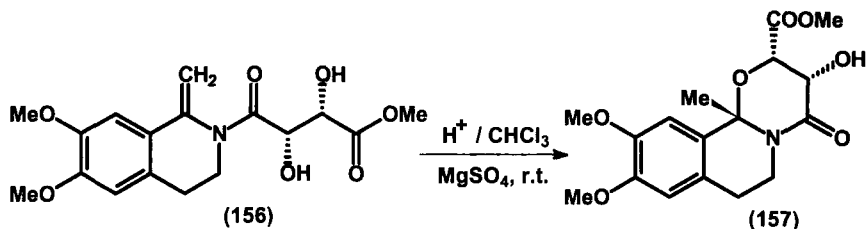
Reduction of hydroxy lactams (**154**) with a complex of DIBAL and butyllithium gave an inseparable mixture of perhydropyrido[2,1-*b*][1,3]oxazines (**155**) (92TL507). When Red-Al was used as a reducing agent, side products

were also formed in comparable amounts. When either epimer of **154** ( $R = \text{allyl}$ ,  $R^1 = \text{OTBS}$ ) was treated with DIBAL, the same mixture of *trans*-fused and *cis*-fused isomers of **155** ( $R = \text{allyl}$ ,  $R^1 = \text{OTBS}$ ) containing the substituents in equatorial positions was formed.

Treatment of 6-chloro-1-(3-hydroxypropyl)-4-phenyl-1,2-dihydropyridin-2-one with sodium methylate in boiling methanol afforded 8-phenyl-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazin-6-one [78GEP2731982; 79JAP(K)79/05997; 81BRP1588166, 81USP4284778].

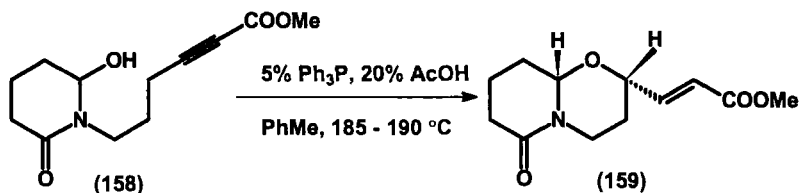
1-(3-Hydroxypropyl)-2-piperidones (e.g., **39**) were cyclized on treatment with aqueous perchloric acid, followed by dehydration heating to give 3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium perchlorates (e.g., **38**) [60JA5148; 70JCS(CC)900; 79TL809]. 1-(3-Hydroxypropyl)-3,5-dimethyl-2-piperidone could not be similarly cyclized (60JA5148). Hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium perchlorate (**38**) and its 7,8-tetramethylene derivative were also prepared by cyclization of *N*-(3-chloropropyl)-2-piperidone and its 4,5-tetramethylene derivative (75CJC2791).

2,3,4,6,7,11*b*-Hexahydro[1,3]oxazino[2,3-*a*]isoquinolines and a 11*b*-methyl derivative (66AP817) were prepared from 2-(3-hydroxypropyl)-3,4-dihydroisoquinolinium bromides and a 1-methyl derivative with an aqueous base (66AP817; 85AJC1591). 1-Methylenetetrahydroisoquinoline (**156**) gave [1,3]oxazino[2,3-*a*]isoquinolin-4-one (**157**) in acidic chloroform [92H(34)943].

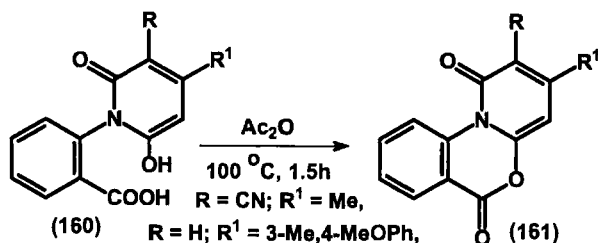


### 3. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]

Cyclization of the piperidone derivative (**158**) gave rise to diastereomerically pure perhydropyrido[2,1-*b*][1,3]oxazin-6-one (**159**) (94JA10819). Heating 1-(3-methoxy-1-propyl)-2-hydroxy-3-cyano-4-methylpyridin-6(1*H*)-one in 25% sulfuric acid at 80°C for 2 h gave 8-methyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazine-9-carboxamide (89EUP316779). 8-(4-Methoxyphenyl)-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]oxazine-2,6-dione was obtained by cyclization of 3-[4-(4-methoxyphenyl)-2,6-dioxo-1,2,3,6-



tetrahydro-1-pyridyl]propionic acid in boiling acetic anhydride (93JIC261). Heating the benzoic acid derivatives **160** in acetic anhydride afforded pyrido[1,2-*a*][3,1]benzoxazine-1,6-diones (**161**) [81IJC(B)1050; 93CCCC1953]. 1-(2-Carboxyethyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolinone was cyclized to 3-oxo-2,3,7,8,9,10-hexahydro-1*H*-[1,3]oxazino[3,2-*a*] quinolinium chloride by heating in acetyl chloride at 50°C (69MI1).



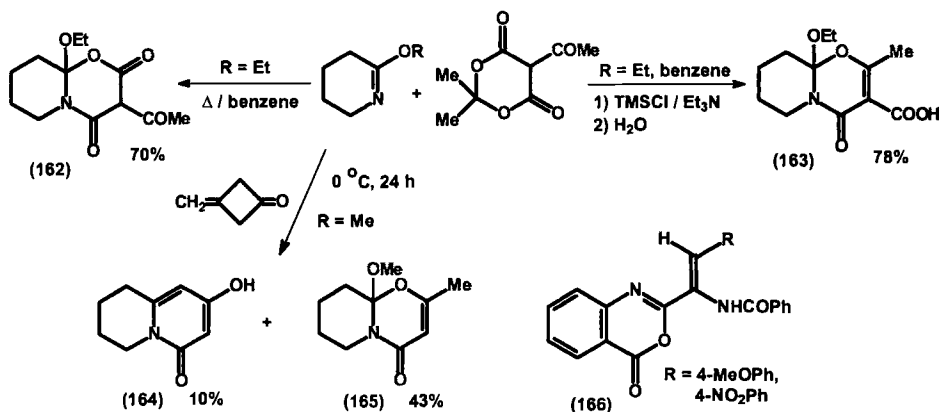
#### 4. By Formation of Two Bonds from [4 + 2] Atom Fragments

The reaction of 1-ethoxy-2-methylpropene and 1-chloromethyl-2(1*H*)-piperidone gave 2-methoxy-3,3-dimethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazonium chloride (91ZOB2743).

Depending upon the reaction conditions, 2-ethoxy-3,4,5,6-tetrahydropyridine and isopropylidene 2-acetylmalonate afforded either perhydropyrido[2,1-*b*][1,3]oxazine-2,4-dione (**162**) or hexahydropyrido[2,1-*b*][1,3]oxazine-3-carboxylic acid (**163**) (86MI1). Reaction of 2-methoxy-3,4,5,6-tetrahydropyridine with diketene without a solvent gave a mixture of 4*H*-quinazolin-4-one (**164**) and hexahydropyrido[2,1-*b*][1,3]oxazin-4-one (**165**) [75H(3)927].

Diels-Alder reactions of 2-styryl-4*H*-1,3-benzoxazin-4-ones and maleic anhydride at 140°C gave 7-aryl-7,8,9,11-tetrahydropyrido[2,1-*b*][1,3]benzoxazin-11-ones [91IJC(B)754], but in boiling xylene 7-*o*-bromophenyl-11-oxo-7,8,9,11-tetrahydropyrido[2,1-*b*][1,3]benzoxazine-8,9-dicarboxylic acid was obtained from 2-(2-*o*-bromophenylvinyl)-4*H*-1,3-benzoxazin-4-one (96MI2).

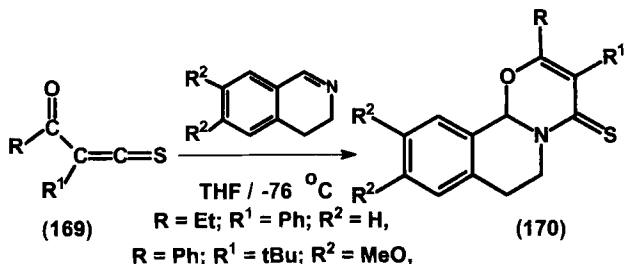
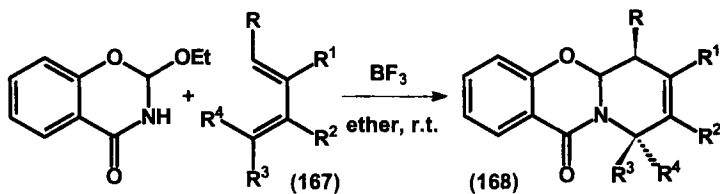
Di(2,2,2-trichloroacetyl)carbodiimide, formed *in situ* from trichloro-



acetyl isocyanate, reacted with quinoline to yield 1-(2,2,2-trichloroacetyl)imino-3-trichloromethyl-1*H*,4*aH*-[1,3]oxazino[3,2-*a*]quinoline (73IZV-456).

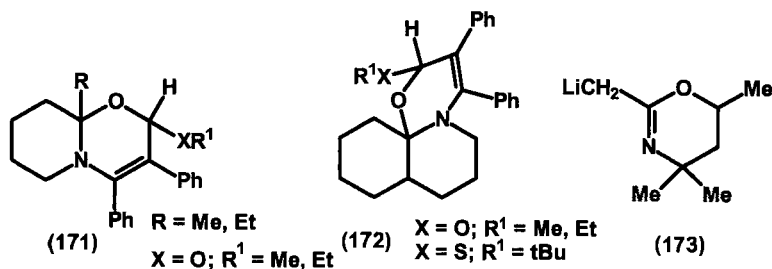
6-Oxopyrido[1,2-*a*][3,1]benzoxazine-1,2-dicarboxylates (**70**) were obtained in the reactions of 3,1-benzoxazinones (**166**) and diethyl maleate in boiling xylene [89IJC(B)126; 90MI1, 90RRC55; 92MI3].

Cycloaddition of 2-ethoxy-2,3-dihydro-4*H*-1,3-benzoxazin-4-one with conjugated diene **167** gave tetrahydropyrido[2,1-*b*][1,3]oxazin-6-ones (**168**) (71JHC865). Diels-Alder reactions of 3,4-dihydroisoquinolines and thioketenes (**169**), formed *in situ*, yielded 4,6,7,11*b*-tetrahydro[1,3]oxazino[2,3-*a*]isoquinoline-4-thiones (**170**) [83AG(E)55; 88CB1165].



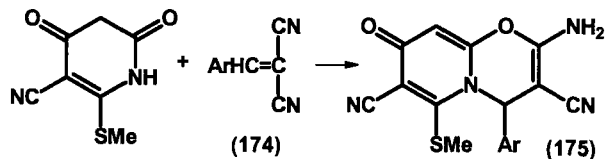
### 5. By Formation of Two Bonds from [3 + 3] Atom Fragments

Reaction of the silver salt of 2-pyridone with 1,3-diiodopropane in boiling dioxan gave 3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]oxazinium iodide (60CB61). Reactions of 2-pyridone (78LA1655; 79CB1585; 88CB951), 2-piperidone [82ZN(B)222; 88CB951], and 2-quinolones (76M859; 79CB1585) with malonyl dichlorides (76M859; 78LA1655) and chlorocarbonylketenes [79CB1585; 82ZN(B)222; 88CB951] afforded mesoionic compounds **54** [ $R^1 = R^2 = R^3 = H$ , and  $R^2 = R^3 = -(CH=CH)_2-$ ] and **59**. 4-Hydroxyquinolin-2(1*H*)-one reacted with malonyl chlorides and bis(2,4,6-trichlorophenyl) malonates to give pyranoquinolines instead of mesoionic [1,3]oxazino[3,2-*a*]quinolines [**54**,  $R^1 = OH$ ,  $R^2 = R^3 = -(CH=CH)_2-$ ] (76M859).



Reactions of diphenylcyclopropenone with 2-alkyl-3,4,5,6-tetrahydropyridines and 2,3,4,4*a*,5,6,7,8-octahydroquinoline in an alcohol or in *tert*-butyl mercaptan afforded hexahydropyrido[2,1-*b*][1,3]oxazines (**171**) and [1,3]oxazino[2,3-*j*]quinolines (**172**), respectively (86S899).

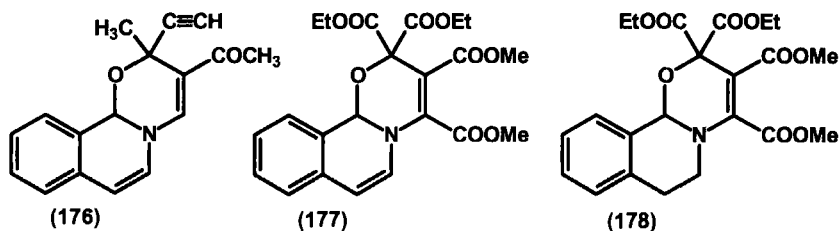
2,4,4-Trimethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrido[2,1-*b*][1,3]oxazonium salt was prepared in the reaction of lithio salt (**173**) and 1,3-dibromopropane in THF at room temperature (73JOC36).



Cyclocondensation of 6-methylthio-5-cyano-1,2,3,4-tetrahydropyridine-2,4-dione with arylidenemalononitrile (**174**) in the presence of piperidine in boiling ethanol gave 2-amino-4-aryl-6-methylthio-8-oxo-4,8-dihydropyrido[2,1-*b*][1,3]oxazine-3,7-dicarbonitrile (**175**) (92MI4).

### 6. By Formation of Three Bonds from [2 + 2 + 2] Atom Fragments

[1,3]Oxazino[2,3-*a*]isoquinoline (**176**) could be isolated in 1% yield from an ethereal reaction mixture of acetylacetylene and isoquinoline [75JCS(P1)446]. [1,3]-Oxazino[2,3-*a*]isoquinolinetetracarboxylates (**177**) and (**178**) were obtained when reaction mixtures of isoquinoline or 3,4-dihydroisoquinoline and diethyl ketomalonate were treated with dimethyl acetylenedicarboxylate in benzene at room temperature (67CB1094).



### 7. Ring Transformation

Heating 10-oxo-5-aza-4,10-dioxo-9-ethoxycarbonylcyclodecane (**34**) in xylene for 4 h with the removal of water afforded ethyl 4-oxo-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]oxazine-9-carboxylate (**33**) in 20% yield (67ZOB1703).

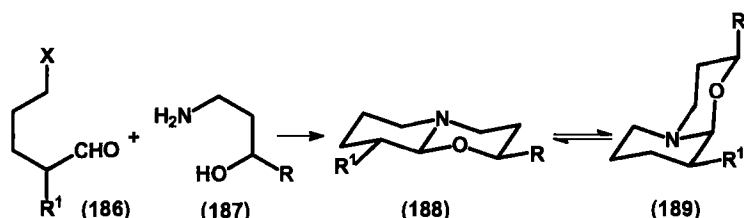
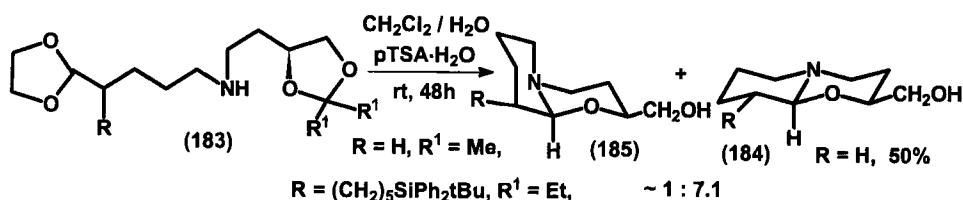
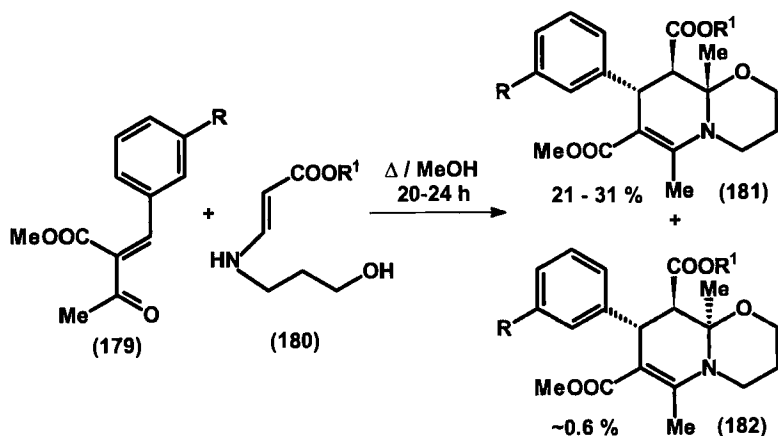
### 8. Miscellaneous

Reaction between  $\alpha,\beta$ -unsaturated ketone (**179**) and enamine (**180**) furnished a complex reaction mixture that contained diastereomeric pyrido[2,1-*b*][1,3]oxazinedicarboxylates (**181**) and (**182**) (92MI1).

Treatment of **183** ( $R = H$ ,  $R^1 = Me$ ) with *p*-toluenesulfonic acid monohydrate in methylene chloride gave 2-hydroxymethylperhydropyrido[2,1-*b*][1,3]oxazine (**184**;  $R = H$ ) (92T6325). Similar reaction of **183** [ $R = (CH_2)_5SiPh_2-t-Bu$ ,  $R^1 = Me$ ] in the presence of water, followed by treatment with saturated aqueous sodium hydrogen carbonate yielded ca. 7–10:1 mixture of **184** [ $R = (CH_2)_5SiPh_2-t-Bu$ ] and **185** [ $R = (CH_2)_5SiPh_2-t-Bu$ ] (95JOC2989).

Cyclocondensation of 5-halovaleraldehydes (**186**) and 1,3-amino alcohols (**187**) gave equilibrium mixtures of *trans*- and *cis*-pyrido[2,1-*b*][1,3]oxazines (**188** and **189**), with a predominance of the *trans*-fused bicycle; both diastereomers contained the substituent in the equatorial position (90TL4281; 94JA2617, 94JOC6904). However, kinetic selectivity for the formation of *cis*-pyrido[2,1-*b*][1,3]oxazine (**189**) was exhibited versus the *trans* compound **188** in the case of the dimethyl derivative ( $R = R^1 = Me$ ) (90TL4281).

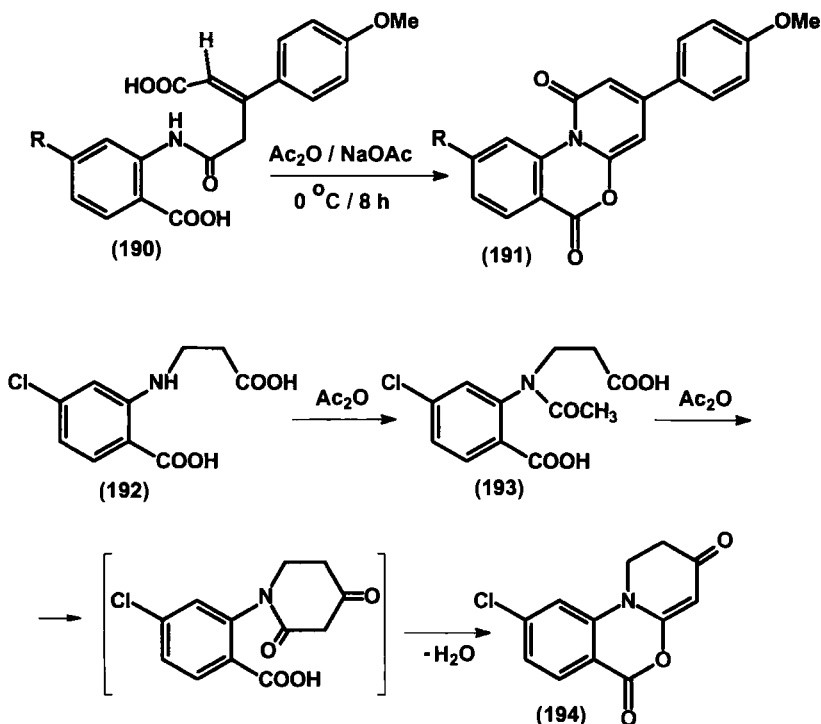




Reactions of 1,3-amino alcohols with glutaraldehyde and KCN in a phosphate buffer at pH 3–4 gave 6-cyanoperhydropyrido[2,1-*b*][1,3]oxazines (46, R = H, *n*-Bu) [71JOC226; 88H(27)1575]. Replacement of KCN by ethanethiol led to 6-ethylthioperhydropyrido[2,1-*b*][1,3]oxazine in 88% yield (71JOC226). 6-Cyano-8-methylperhydropyrido[2,1-*b*][1,3]oxazine was prepared in an exothermic reaction of 3-methylglutaraldehyde dicyanohydrin and 3-aminopropanol in water (68USP3375249). Cyclocondensation of 3-aminopropanol and 4-benzoylbutyric acid and its 2- and 3-substituted derivatives in boiling toluene, xylene, or chlorobenzene in the presence of *p*-toluenesulfonic acid and a Dean–Stark tube yielded 9*a*-phenylperhydropyrido[2,1-*b*][1,3]oxazin-6-ones (65BEP659529; 67USP 3334095; 69JOC165; 76JMC436). Reaction of equivalent amounts of 3-

aminopropanol and methyl 4-acetylbutyrate in boiling dichloromethane or toluene in a Dean-Stark apparatus gave 9*a*-methylperhydropyrido[2,1-*b*][1,3]oxazin-6-one [91JCS(P2)735]. Cyclization of *N*-(3-hydroxypropyl)-5-aminopentanol in the presence of Raney Ni afforded perhydropyrido[2,1-*b*][1,3]oxazine (72BSF4736). Perhydropyrido[2,1-*b*][1,3]oxazin-4-one and perhydropyrido[2,1-*b*][1,3]oxazine were obtained by the cyclization of *N*-(5,5-diethoxypentyl)-3-hydroxypropionamide and *N*-(5,5-diethoxypentyl)-3-aminopropanol, respectively (61AP65).

Heating a mixture of 2-(carboxymethyl)benzoic acids and 3-aminopropanol in *o*-dichlorobenzene in the presence of *p*-toluenesulfonic acid yielded 2,3,4,6-tetrahydro[1,3]oxazino[3,2-*b*]isoquinolin-6-ones (78BEP 866987, 78GEP2756067; 79CPB2372). Similar reaction between *o*-benzoylphenylacetic acid and 3-aminopropanol in toluene resulted in 11*b*-phenyl-2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinolin-6-one (71MI1). Reaction of 2-(2-bromoethyl)benzaldehyde and 3-aminopropanol in ethanol led to 2,3,4,6,7,11*b*-hexahydro[1,3]oxazino[2,3-*a*]isoquinoline (61AP645).



1*H*,6*H*-Pyrido[1,2-*a*][3,1]benzoxazine-1,6-diones (**191**) were obtained by the cyclization of anthranilic acid derivatives (**190**) (89SC3103). Heating either anthranilic acid derivatives **192** or **193** in acetic anhydride afforded pyrido[1,2-*a*][3,1]benzoxazine-3,6-dione (**194**) in 33% and 55% yield, respectively (70KGS879).

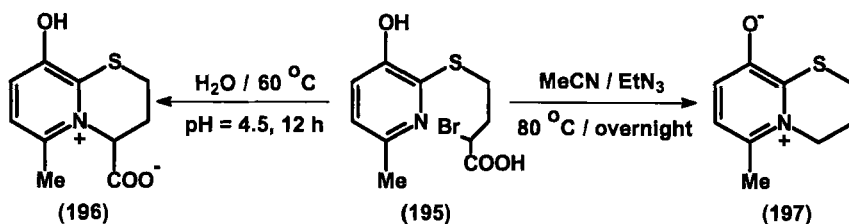
## B. PYRIDO[2,1-*b*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

### 1. By Formation of One Bond $\alpha$ to the Bridgehead

Nitrogen Atom [6 + 0( $\alpha$ )]

3-Hydroxy-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-5-ium chloride was formed when 2-hydroxy-3-(2-pyridylthio)propyl chloride was stirred in methylene chloride overnight (92JOC6335). When the reaction was carried out in methanolic sodium methylate, 3-(2-oxo-1,2-dihydro-1-pyridyl)thietane was obtained in 58% yield.

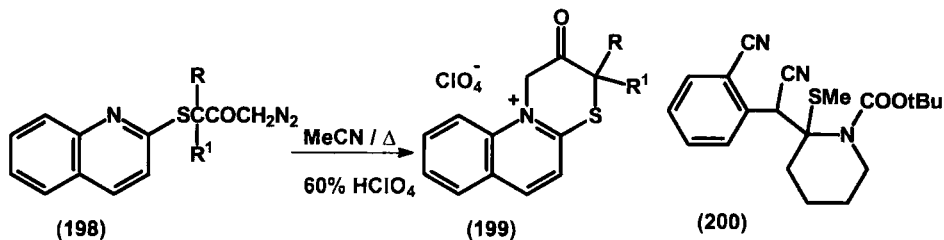
Cyclization of 2-oxo-3-(2-pyridylthio)propyl chloride on the action of excess potassium iodide afforded 3,3-dihydroxy-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium iodide, from which the 3-oxo derivative **89** was obtained in quantitative yield by heating *in vacuo* (80CL947).



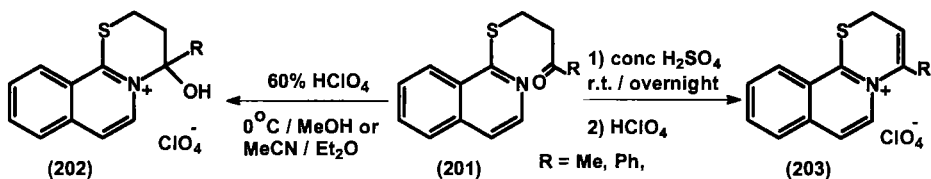
Cyclization of 2-bromo-4-(2-pyridylthio)butyric acid hydrobromide (**195**) in water at pH 4.5 at 60°C gave pyrido[2,1-*b*][1,3]thiazinium betaine (**196**), whereas decarboxylated betaine (**197**) was formed when the cyclization was carried out in acetonitrile in the presence of triethylamine (73ACS1059). When the *R* enantiomer of **195** was cyclized in water in the absence of bromide ion, the *S* enantiomer of the bicycle **196** was obtained in 9% yield without racemization. However, in the presence of bromide ion, bromide exchange of the starting carboxylic acid **195** with bromide ion led to partial racemization.

7-Acetyl-3-hydroxy-6-methyl-8-phenyl-2,3,4,8-tetrahydropyrido[2,1-*b*]-[1,3]thiazine-9-carbonitrile was prepared by the cyclization of 5-acetyl-3-

cyano-2-[(3-chloro-2-hydroxypropyl)thio]-6-methyl-4-phenyl-1,4-dihydropyridine with sodium methylate (94KGS139).



Treatment of diazocarbonyl derivatives **198** with 60% perchloric acid gave [1,3]thiazino[3,2-*a*]quinolinium perchlorates **(199)** (84KGS635; 85KFZ804). Treatment of thiazine **(200)** with trifluoroacetic acid resulted in the formation of 6-imino-2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinoline-11-carbonitrile (96JHC1791). Similarly, 8-aryl-6-imino-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]thiazine-7-carbonitriles were prepared from 3-(*tert*-butoxycarbonyl)-2-(2-aryl-3,3-dicyanoallylidene)perhydro-1,3-thiazines (96JHC1791).



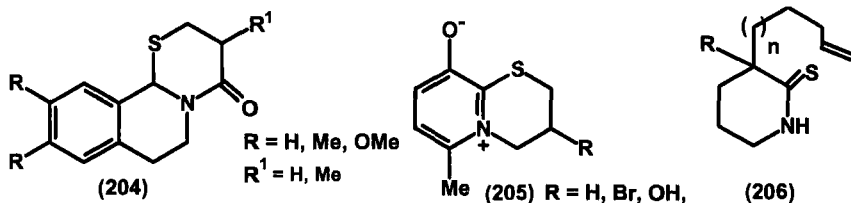
Cyclization of 1-isoquinolyl derivatives **(201)** in a cold solution of perchloric acid or in conc. sulfuric acid at room temperature afforded 4-hydroxy-3,4-dihydro-2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium perchlorates **(202)** and 2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium salts **(203)**, respectively (74IJC1242). Heating 1-[(3-phenyl-3-hydroxypropyl)thio]isoquinoline in PPA yielded the 1-phenyl-3,4-dihydro-2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium salt (74IJC1242). 6,7-Dihydro derivatives of 2*H*-[1,3]thiazino[2,3-*a*]isoquinolinium perchlorate **(203, R = Me)** and 4-methyl-2,3,4,6,7,11*b*-hexahydro-[1,3]thiazino[2,3-*a*]isoquinoline were obtained by cyclization of the 3,4-dihydro derivative of **201** ( $\text{R} = \text{Me}$ ) and 4-[(1,2,3,4-tetrahydroisoquinolin-1-yl)thio]-2-butanol, respectively, in conc. sulfuric acid or in PPA [81IJC(B)372].

## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [ $6 + 0(\beta)$ ]

2,3,4,6-Tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-one was formed when *N*-(3-mercaptopropyl)homophthalimide was heated in *o*-dichlorobenzene in the presence of *p*-toluenesulfonic acid at 120°C (78BEP866987, 78GEP2756067; 79CPB2372). Treatment of *N*-(*o*-acetylthioxybenzoyl)-valerolactam with silver acetate and pyridine in methanol gave 5*a*-hydroxypyrido[2,1-*b*][1,3]benzothiazin-11-one (**25**) (68AG909).

## 3. By Formation of Two Bonds from [ $4 + 2$ ] Atom Fragments

Reaction of 4-phenyl-6-chloro-2(1*H*)-pyridone and 3-aminopropanethiol on heating in ethylene glycol at 190–200°C afforded 8-phenyl-2,3,4,6-tetrahydropyrido[2,1-*b*][1,3]thiazin-6-one (79CPB1207). 2,3,4,6,7,11*b*-Hexahydro[1,3]thiazino[2,3-*a*]isoquinolin-4-ones (**204**) were obtained in the reactions of 3,4-dihydroisoquinolines and 3-mercaptopropionic acid in the presence of *p*-toluenesulfonic acid (69FRP155211; 87MI1).

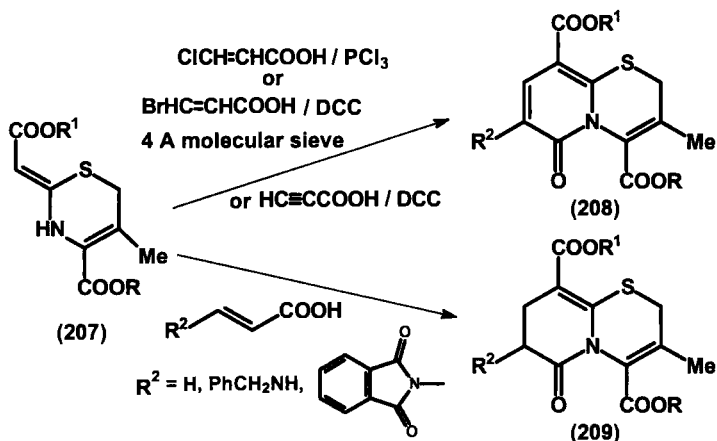


Reaction of 2-cyanomethyl-4*H*-1,3-benzothiazin-4-one with benzoylacetone at 160°C yielded 8-cyano-7-imino-9-phenyl-7*H*,11*H*-pyrido[2,1-*b*][1,3]benzothiazin-11-one (85MI1; 86MI2). Reaction of 2-ethoxy-2,3-dihydro-4*H*-1,3-benzothiazin-4-one with 1,2,3,4-tetramethylbutadiene and 2,4-dimethyl-1,3-pentadiene in the presence of boron trifluoride in diethyl ether gave rise to 6,7,8,9-tetramethyl- and 7,9,9-trimethyl-5*a*,6,9,11-tetrahydropyrido[2,1-*b*][1,3]benzothiazin-11-one, respectively (73JHC149).

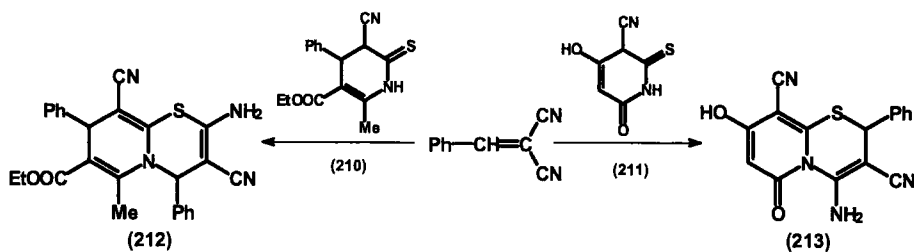
## 4. By Formation of Two Bonds from [ $3 + 3$ ] Atom Fragments

Reactions of 3-hydroxy-6-methyl-2(1*H*)-pyridinethione with 1,3-dibromopropanes in methanol in the presence of sodium methylate yielded betaines (**205**) (70ACS2949). 9-Hydroxy-3,4-dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium bromide was obtained in the reaction of 3-hydroxypyridine-2(1*H*)-thione and 1-bromo-3-chloropropane in boiling toluene [81JCR(S)208].

*Anhydro* 4-hydroxy-2-oxo-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxides (**128**) were prepared in the reactions of 2(1*H*)-pyridinethione with carbon suboxide and monosubstituted malonyl dichlorides (72S312). Reaction of 2-piperidonethione and its 3-monosubstituted derivatives with carbon suboxide [94H(39)219; 95H(41)1631], prepared from dibromomalonyl dichloride with zinc dust in diethyl ether at  $-78^{\circ}\text{C}$ , with malonyl dichloride [94H(39)219; 95H(41)1631], and with (chlorocarbonyl)phenylketene [94H(39)219; 95H(41)1631, 95JOC3795] afforded 9-(un)substituted 2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazine-2,4-diones and their 3-phenyl derivatives, whereas reaction of 3,3-disubstituted 2-piperidonethiones with carbon suboxide (95T6651; 96TL335), with monosubstituted malonyl dichlorides [93JOC5040; 94H(39)219; 95H(41)1631, 95JOC3795, 95T6651], and with (chlorocarbonyl)phenylketene (95JOC3795, 95S973, 95T6651) gave *anhydro* 9,9-disubstituted 4-hydroxy-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxides and their 3-substituted derivatives (e.g., **113** and **124**). From the reaction mixture of 3-methyl-2-piperidinethione and carbon suboxide *anhydro* 9-methyl-4-hydroxy-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxide could be also isolated in 15% yield, as well as 9-methyl-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazine-2,4-dione (85%) [94H(39)219; 95H(41)1631]. The former easily gave the latter by proton migration. Depending upon the reaction circumstances when a double or triple bond in the  $\beta$ - or  $\gamma$ -position was present in the one of the 3-side chains of 3,3-disubstituted 2-piperidinethiones (e.g., **119** and **206**) the primarily formed *anhydro* 4-hydroxy-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium hydroxides spontaneously underwent [4 + 2]-cycloaddition to give cycloaddition products or polycondensed products (e.g., **115**, **121**, and **123**) formed by COS elimination from cycloaddition products (93JOC5040; 95JOC3795, 95S973; 96TL335).



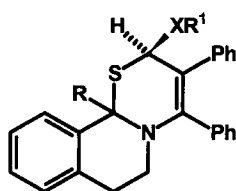
6-Oxopyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylates (**208**;  $R = Et, CH_2Ph$ ;  $R^1 = Et, CH_2Ph$ ) were prepared either in the reactions of thiazines (**207**;  $R = Et, CH_2Ph$ ;  $R^1 = Et, CH_2Ph$ ) with chloroacrylic acid in the presence of phosphorus trichloride in a boiling mixture of benzene and dioxane, or with propiolic acid in the presence of DCC in methylene chloride at ambient temperature, or with (*Z*)-3-bromoacrylic acid in the presence of DCC and a 4-Å molecular sieve in methylene chloride [81JCS(CC)395; 91JCS-(P1)3077]. From the latter reaction, other monocyclic thiazines could also be isolated. The reaction of thiazine (**207**;  $R = R^1 = CH_2Ph$ ) with phthalimidoacryloyl chloride in boiling chloroform in the presence of triethylamine or with phthalimidoacrylic acid in methylene chloride in the presence of DCC at room temperature overnight furnished pyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate (**209**;  $R = R^1 = CH_2Ph$ ;  $R^2 =$  phthalimido) in 28–30% yield [91JCS(P1)3077]. Better yields (56–92%) of **209** ( $R = R^1 = CH_2Ph$  or  $Et$ ;  $R^2 = H, phthalimido, PhCH_2NH$ ) could be achieved when the appropriate acrylic acid was used in a boiling mixture of benzene and dioxane in the presence of phosphorus trichloride under nitrogen.



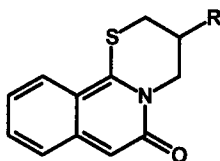
Cyclocondensations of benzyldenemalononitrile with pyridinethiones **210** and **211** afforded the amino derivatives of pyrido[2,1-*b*][1,3]thiazines **212** and **213**, respectively (90MI2; 92MI6). Reaction of 5-acetyl-3-cyano-6-methyl-4-phenyl-3,4-dihydropyridine-2(1*H*)-thione with epichlorohydrin in the presence of potassium hydroxide and sodium methylate gave 7-acetyl-3-hydroxy-6-methyl-8-phenyl-2,3,4,8-tetrahydropyrido[2,1-*b*][1,3]-thiazine-9-carbonitrile (94KGS139).

2,3,4,6,7,8-Hexahydropyrido[2,1-*b*][1,3]thiazin-4-one (**99**) and its 9-pent-4-enyl or 9-(6-trimethylsilanylhexas-4-enyl) derivatives were prepared when the appropriate piperidine-2-thione reacted with acryloyl chloride in 1,2-dimethoxyethane [94H(37)441].

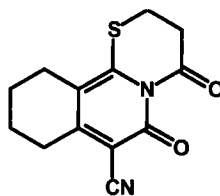
Reaction of piperidine-2-thione and diphenylcyclopropanone in acetonitrile gave 2,3-diphenyl-2,3,4,6,7,8-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one in 88% yield [71LA(752)136]. 2,6,7,11*b*-Tetrahydro[1,3]thiazino[2,3-*a*]isoquinolines (**214**) were obtained from 1-substituted 3,4-dihydroisoquino-



(214)  $X = O$   $R^1 = \text{Me, Et}$   
 $X = S$   $R^1 = t\text{Bu}$



(215)  $R = \text{H, OH}$



(216)

lines on treatment with diphenylcyclopropenethione in an alcohol or in the presence of *tert*-butylmercaptan [79AX(B)1285, 79TL1213; 86S899]. If the reactions were carried out in dimethoxyethane at room temperature, pyrrolo[2,1-*a*]isoquinoline-1-thiones formed.

Tetrahydro[1,3]thiazino[2,3-*a*]isoquinolin-6-ones (**215**) were prepared in the reactions of 3-hydroxy-1-mercaptoisoquinoline with 1,3-dibromopropane and 1,3-dibromopropan-2-ol in methanolic sodium methylate at 50°C (72ACS1620).

Reaction of 1-mercapto-4-cyano-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one with 3-bromopropionic acid in boiling ethanol in the presence of sodium acetate gave octahydro[1,3]thiazino[2,3-*a*]isoquinoline-4,6-dione (**216**) (89PS203).

See Section III.B.6 for further examples.

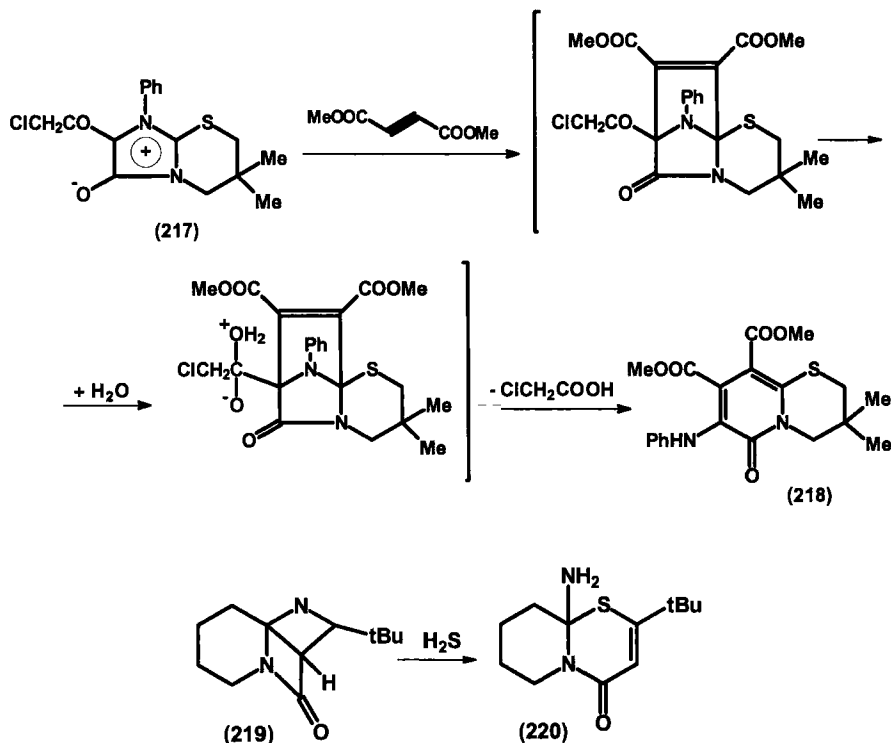
## 5. Ring Transformations

Reaction of mesoionic imidazo[2,3-*b*][1,3]thiazine (**217**) and dimethyl acetylenedicarboxylate produced tetrahydropyrido[2,1-*b*][1,3]thiazin-6-one (**218**) [88H(27)227]. 6-Oxopyrido[2,1-*b*][1,3]thiazine-4,9-dicarboxylate (**208**;  $R = R^1 = \text{Et}$ ,  $R^2 = \text{H}$ ) was obtained in 73% yield when thiazetidene (**138**;  $R = R^1 = \text{Et}$ ,  $R^2 = \text{H}$ ) was stirred in benzene in the presence of Wilkinson's catalyst, tris(triphenylphosphine)rhodium(I) chloride, under hydrogen overnight (84TL4157; 92T10149). Reaction of Dewar pyrimidinone (**219**;  $R = t\text{-Bu}$ ,  $R^1 = \text{H}$ ) with hydrogen sulfide gave a *ca.* 2:1 mixture of 9*a*-amino-2-*tert*-butyl-4,6,7,8,9,9*a*-hexahydropyrido[2,1-*b*][1,3]thiazin-4-one (**220**) and 2-*tert*-butyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [89JCS(P)1231].

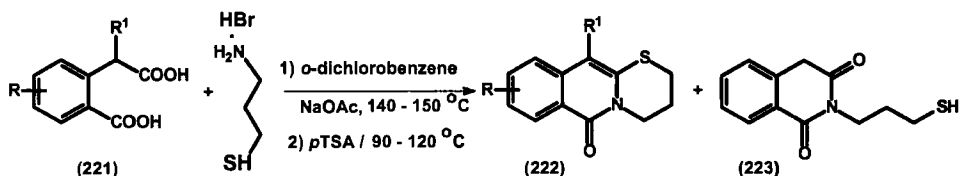
## 6. Miscellaneous

The reactions of homophthalic acids or  $\alpha$ -alkyl,  $\alpha$ -phenyl, and  $\alpha$ -benzyl derivatives (**221**) and 3-aminopropanethiol hydrobromide in *o*-

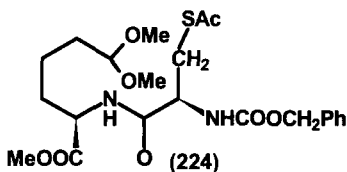




dichlorobenzene in the presence of sodium acetate, with the removal of water by azeotropic distillation, and then in the presence of *p*-toluenesulfonic acid, afforded 2,3,4,6-tetrahydro[1,3]thiazino[3,2-*b*]isoquinolin-6-ones (**222**) [78BEP866987, 78GEP2756067; 79CPB2372, 79JAP(K)79/84597]. When the reaction of **221** ( $R = R^1 = H$ ) was carried out in boiling acetic acid overnight both [1,3]thiazino[3,2-*b*]isoquinolin-6-one (**222**;  $R = R^1 = H$ ) and *N*-(3-mercaptopropyl)homophthalimide (**223**) were isolated from the reaction mixture (79CPB2372). Reaction of ethyl 2-cyanomethylenecyclohexanecarboxylate and 3-aminopropanethiol hydrobromide in boiling *o*-dichlorobenzene in the presence of sodium acetate gave 3,4,7,8,9,10-



hexahydro-2*H*,6*H*-1,3-thiazino[3,2-*b*]isoquinolin-6-one (81USP4284778). Reaction of 4-benzoylbutyric acid and 3-aminopropanethiol gave 9*a*-phenylperhydropyrido[2,1-*b*][1,3]thiazin-6-one (65BEP659528; 67USP 3334091). Treatment of methyl (*S*)-2-[*N*-[(phenylmethoxy)carbonyl-*S*-acetyl-L-cysteinyl]amino]-6,6-dimethoxyhexanoate (**224**) with sodium methylate in methanol for 20 min, then with Amberlyst 15 ion exchange resin in dichloromethane for 3 h at room temperature afforded 3-acylamino-4-oxoperhydropyrido[2,1-*b*][1,3]thiazine-6-carboxylate (**109**) (94EUP629627; 96USP5508272).

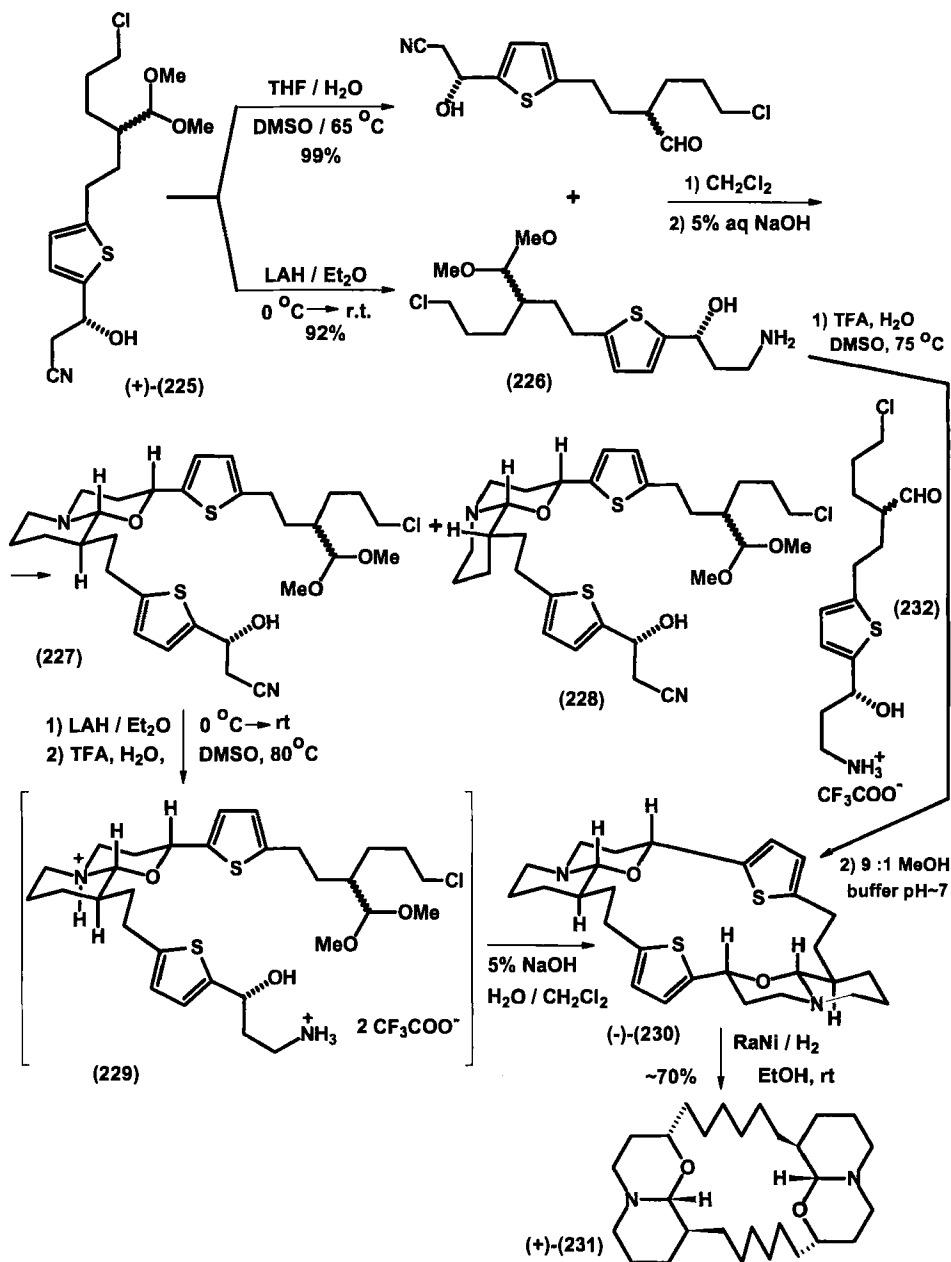


## V. Applications and Important Compounds

### A. PYRIDO[2,1-*b*][1,3]OXAZINES AND THEIR BENZO DERIVATIVES

Perhydropyridol[2,1-*b*][1,3]oxazines are used in the synthesis of indolizidines (gephyrotoxins and monomorine-I) [88H(27)1575; 91SL44, 91SL878] and histrionicotoxin (91SL44) alkaloids.

Two perhydropyrido[2,1-*b*][1,3]oxazine moieties occur as constituent parts of the members of the xestospongine/araguspongine alkaloid family, isolated from different marine sponges (*Xestospongia*, *Haliclona*, and *Niphates* spp.) [83MI1; 84JAP(K)84/227885, 84TL3227; 89CPB1676, 89TL4149; 92JNP1505; 94JA2617, 94JNP1283, 94JOC6904]. The structures of xestospongine C (83MI1; 84TL3227) and ( $\pm$ )-xestospongine D (96BMC 1313) were determined by X-ray investigations. The absolute configuration of araguspongines was assigned on the basis of applications of Hudson's rule and the Horean method (89CPB1676). Scheme 7 shows the total syntheses of (+)-xestospongine A/(+)-araguspongine D (**231**) [91DIS(B)4849; 94JA2617; 95DIS(B)3770; 96JA12074]. The *cis* isomer (**228**) could be equilibrated with the *trans* isomer (**227**) in the presence of triethylamine at 80°C in CDCl<sub>3</sub> (96JA12074). The *cis* isomer (**228**) gave also *trans*-**229** under identical reaction conditions, (i.e., isomerization occurred during the acid-catalyzed hydrolysis). The effect of pH on the macrocyclization of **227** was studied (Table III). Compound **226** could be directly dimerized to **230** when the aldehyde function of **226** was liberated and the amine was protonated by trifluoroacetic acid and then a DMSO solution of **232** was added



SCHEME 7

TABLE III  
EFFECT OF CONDITIONS ON THE YIELD OF THE MACROCYCLIZATION OF  
*trans*-**227** (96JA12074)

Conc. (mM)	pH	Time(h)	Solvent	Yield (%) of (-)- <b>230</b>
0.008	>12	20	9:1 CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O <sup>a</sup>	70 <sup>b</sup>
1.5	8	3	9:1 MeOH:buffer (pH = 7-8)	76 <sup>c</sup>
1.5	7	12	9:1 MeOH:buffer (pH = 6-7)	81 <sup>c</sup>
1.5	6	120	9:1 MeOH:buffer (pH = 6-7)	85 <sup>c</sup>
2.0 <sup>d</sup>	7	12	9:1 MeOH:buffer (pH = 6-7)	58 <sup>c</sup>

<sup>a</sup> Two-phase reaction mixture.

<sup>b</sup> Isolated yield.

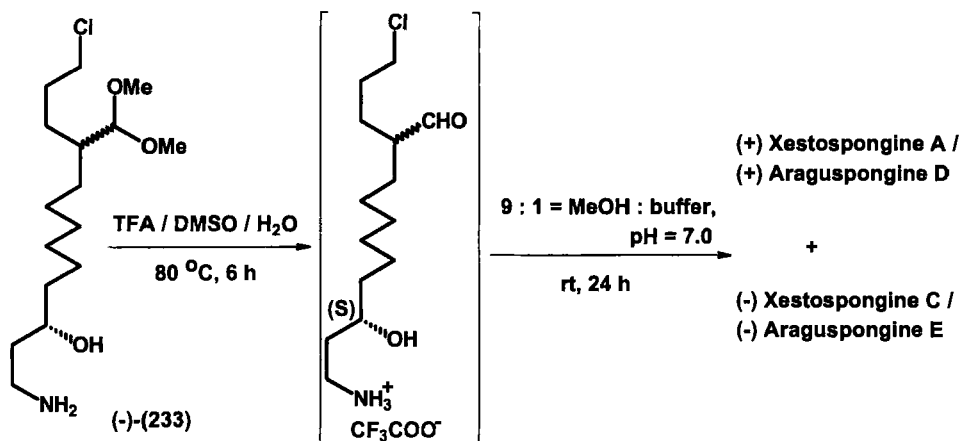
<sup>c</sup> Determined by HPLC.

<sup>d</sup> Starting dimethyl acetal was *cis*-**228**.

into a 9:1 mixture of methanol and buffer (see Table IV) (96JA12074). Starting from (-)-**233**, a 2.2-2.5:1 mixture of (+)-xestospongine A/(+)-araguspongine D and its C-9 epimer (-)-xestospongine C/(-)-araguspongine E was obtained in 50% yield (Scheme 8). The epimers were separated and equilibrated under both acidic (in the presence of excess trifluoroacetic acid) and basic (in the presence of excess triethylamine) conditions at 80°C in CDCl<sub>3</sub> (96JA12074). Thiophene derivative **230** could not be isomerized. From the appropriate starting materials, enantiomers of (+)-xestospongine A/(+)-araguspongine D and epimeric (-)-xestospongine C/(-)-araguspongine E were similarly prepared (96JA12074). Certain members of these alkaloid families showed stronger vasodilative activities than papaverine [83MI1; 84JAP(K)84/227885; 89CPB1676]. Cytotoxic activity of crude extracts of marine sponges were also tested (92MI2; 96BMC1313). (±)-Xestospongine D was found to in-

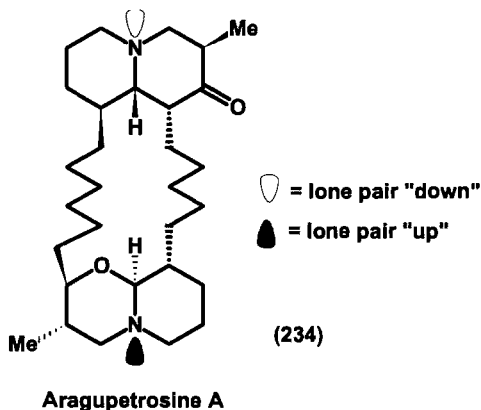
TABLE IV  
EFFECT OF CONCENTRATION ON THE YIELD OF THE MACROCYCLIC  
DIMERIZATION OF **226** AT pH = 7.0 FOR 24 h (96JA12074)

Conc. (mM)	Solvent	Yield (%) of (-)- <b>230</b>
4	100% buffer	31
1	9:1 MeOH:buffer	51
2	9:1 MeOH:buffer	60
10	9:1 MeOH:buffer	53
20	9:1 MeOH:buffer	49
50	9:1 MeOH:buffer	37



SCHEME 8

hibit the growth of certain human cell lines and exhibited antimicrobial activity against the Gram-positive opportunist *Micrococcus luteus* with a minimum inhibitory concentration between 12.5–25  $\mu\text{g}/\text{disk}$  (96BMC1313). Xestospongine B exhibited a high affinity for somatostatin ( $\text{IC}_{50} = 12 \mu\text{M}$ ) (96MI1). The similar aragupetrosine A alkaloid (**234**), isolated from an Okinawan marine sponge *Xestospongia* spp., contains one perhydropyrido[2,1-*b*][1,3]oxazine moiety (89TL4149). Aragupetrosine A showed vasodilative activity.



Dialkyl 7-aryl-6,9a-dimethyl-2,3,4,8,9,9a-hexahydropyrido[2,1-*b*][1,3]-oxazine-7,9-dicarboxylates exhibit long-term antihypertensive-bradycardic, anti-inflammatory, and spasmolytic effects (92MI1).

B. PYRIDO [2,1-*b*][1,3]THIAZINES AND THEIR BENZO DERIVATIVES

(3,4-Dihydro-2*H*-pyrido[2,1-*b*][1,3]thiazinium-3-yl)thio moiety was applied in broad-spectrum antibacterials (86EUP168707, 86EUP169410). 2,3,4,6-Tetrahydro-2*H*,6*H*-[1,3]thiazino[3,2-*b*]isoquinolin-6-ones were investigated and patented as anti-inflammatories and analgesics (78GEP2756067; 79CPB2372, 79YZ880, 79YZ993). [4*S*-[4 $\alpha$ (*R*\*),6 $\alpha$ 9 $\alpha$  $\beta$ ]]-4-Oxoperhydropyrido[2,1-*b*][1,3]thiazine-6-carboxylic acid is a potent inhibitor of angiotensin-converting enzyme and neutral endopeptidase *in vitro* (97JMC1570). epi-16,17-Dihydroeburnamenine (**127**) was prepared via a pyrido[2,1-*b*][1,3]thiazine derivative (96TL335).

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# Enamines as Synthons in the Synthesis of Heterocycles

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I. Introduction .....	283
II. Formation of Small Rings .....	284
III. Five-Membered Rings .....	284
A. Formation of the Pyrrole Ring .....	284
B. Synthesis of Furan and Thiophene Derivatives .....	294
C. Synthesis of Azoles .....	299
D. Other Sulfur- and Phosphorus-Containing Five-Membered Rings .....	305
IV. Six-Membered Rings .....	306
A. Synthesis of Pyridine Derivatives .....	306
B. Cyclization Reactions Leading to Pyrimidines .....	325
C. Other Azines .....	330
D. Synthesis of Substituted Pyrans, Thiopyrans, and Dioxanes .....	333
E. Six-Membered Ring Phosphorus-Containing Heterocycles .....	337
V. Synthesis of Seven- and Eight-Membered Rings .....	338
VI. Enamines as Electron-Rich Synthons in Reactions with Electron-Deficient Azadienes .....	340
VII. Conclusion .....	346
References .....	346

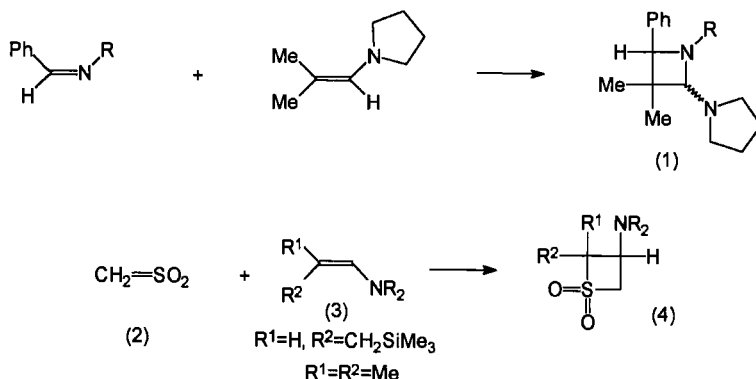
## I. Introduction

Today, studies of the properties and chemical transformations of enamines represent a distinct and fruitful area of organic chemistry. Numerous reviews devoted to the various aspects of enamine chemistry have been published in the last 15 years [82T1975, 82T3363; 83KGS867, 83OPP71; 84RCR651; 85AHC399, 85KGS147; 86T3029; 87MI1; 88H1953, 88MI1, 88ZC345; 89H1409; 90T5423; 91KGS867, 91MI1, 91RCR103; 92AHC1, 92KGS762, 92KGS792; 93CRV1991, 93KFZ(6)37; 94H(37)1233, 94H(38)1127, 94KGS3, 94KGS1603, 94MI1; 95KFZ(12)3]. However, there are no reviews

summarizing the available information on the cyclization of substituted enamines to heterocycles. Our review is intended to fill this gap and presents the results obtained within the last 15 years on the use of enamines in the synthesis of heterocyclic systems. In principle, the order of presentation is based on the type of heterocyclic compound formed by these ring-closure reactions. Special attention has been paid to the pathways of the cyclization reactions involving enamines and their mechanisms.

## II. Formation of Small Rings

Only a few papers on the formation of compounds with small rings have been published. One example is the [2 + 2]-cycloaddition of electron-rich enamines to Schiff bases under high pressure (1.4 GPa) (87JOC365). The reaction leads to substituted azetidines (1). Four-membered ring heterocycles, thietane derivatives (4), are formed by interaction of sulfene (2) with enamines (3) (86CB257; 93JOC3429).



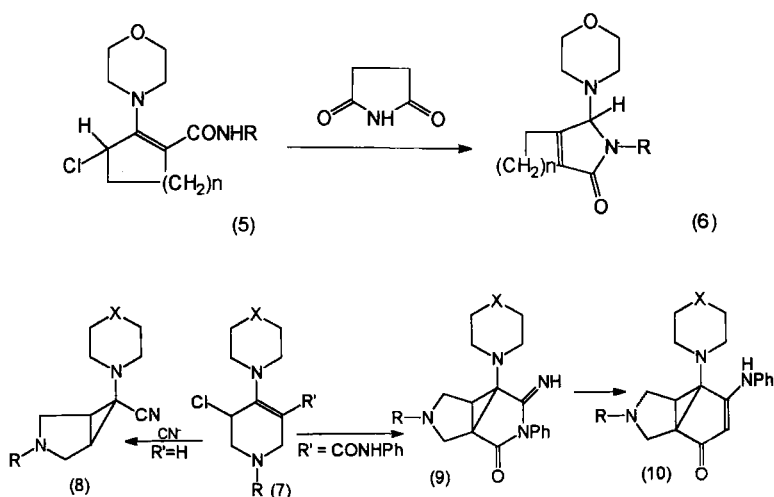
## III. Five-Membered Rings

In comparison with small-ring heterocycles, the publications on the formation of five-membered rings from enamines are quite numerous, with most attention paid to the formation of pyrroles.

### A. FORMATION OF THE PYRROLE RING

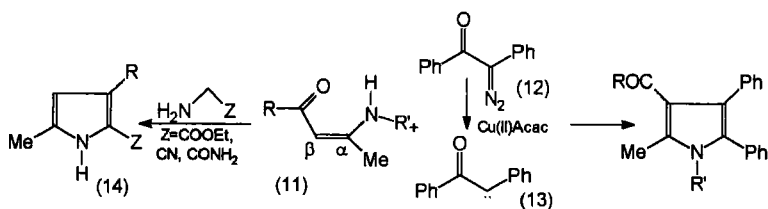
Numerous pyrrole derivatives were synthesized from enamine carbonyl compounds. Cyclic enaminoamides with a chlorine atom in the  $\beta'$ -position

(5) react with succinimide in aqueous acetonitrile at elevated temperatures. The first step in the overall reaction is the formation of condensed cyclopropanes, which subsequently undergo thermal conversion into pyrrolones (6) (89T3189). A reaction utilizing sodium cyanide or sodium borohydride as the nucleophile and *N*-tosylenaminoamides as the enamines is analogous (89T6683). In similar reactions with 4-piperidone derivatives as the starting enamines (7), the piperidine ring rearranges to a pyrrolidine ring (8). When the starting enamine contained an *N*-phenylcarbamoyl group in the  $\beta$ -position, a tricyclic pyrrolidine derivative (9) was obtained. A subsequent Dimroth rearrangement of 9 gives 10 as the final product (89T131; 90T8117).

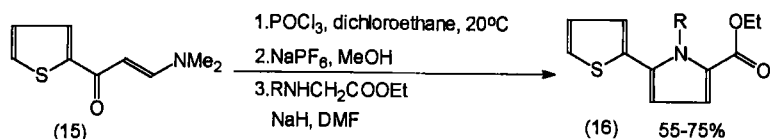


Reaction of enaminoketones (11) with diazoketones (12) in the presence of copper(II) acetylacetonate leads to substituted pyrroles (88JOC2084). In the first step of the reaction sequence, 12 yields a ketocarbene (13), which subsequently attacks the nitrogen and/or the  $\beta$ -carbon in the enaminoketone followed by cyclization with elimination of water. An analogous cyclization with the formation of substituted pyrroles is observed in the reaction of carboethoxycarbene with enaminocarbonyl compounds (95JHC1355). Another possible use of enaminoketones (11) for the synthesis of pyrroles involves their reaction with esters of amino acids and similar compounds (90H1049). The first step is a transamination (80–90% yield). Substituted pyrroles (14) are then obtained by Dieckmann cyclization in the presence of sodium ethoxide or pyridine (moderate yields). Pyrroles can also be obtained from enamines with an aldehydic group present in the substituent on the enamine nitrogen atom (95JHC871).

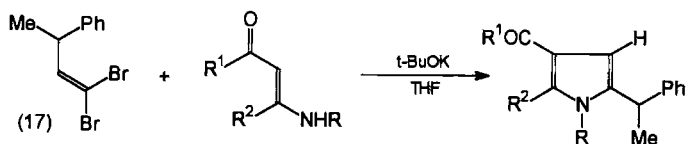




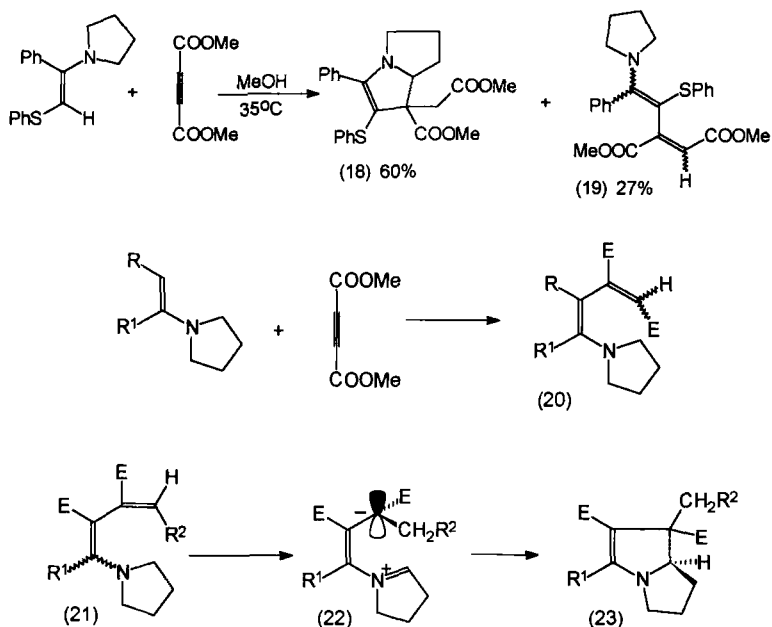
Another approach leading to pyrroles from enaminoketones was demonstrated [94H(37)487]. An enamine with the thiophene ring (**15**) was converted into an imido chloride vinyllog, which interacts with esters of amino acids in the presence of sodium hydride in dimethylformamide and affords



derivatives of 2-(2-thienyl)pyrrole (**16**). The interaction of enaminoketones and enamino esters with 1,1-dibromo-3-phenyl-1-butene (**17**) in the presence of potassium *tert*-butoxide in tetrahydrofuran involves [3 + 2]-cyclocondensation via initial dehydrobromination followed by  $S_N2'$  substitution and the aza-Claisen rearrangement and cyclization in tandem (94SL1007).

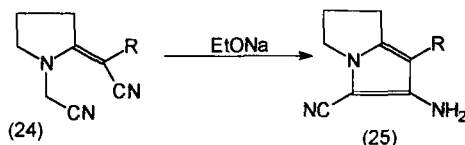


There are numerous studies on the synthesis of pyrrolizines from enamines. In these reactions, one of the steps is the closure to a new hydrogenated pyrrole ring. In polar solvents, the reaction of enamines with dimethyl acetylenedicarboxylate follows two different pathways, the formation of cycloadducts (**18**) and Michael adducts (**19**) (81T3525). Subsequent studies of this reaction have demonstrated (by low-temperature  $^1\text{H}$  NMR) that compounds of the type **20** are intermediates in this cyclization (83JA4775). On the basis of this information (83JA4775), the authors then studied this type of cyclization using dienamines (**21**). The reaction follows the scheme shown, with a [1,6] antarafacial hydrogen shift and the formation of a dipole-



lar structure (22), followed by disrotatory electrocyclization leading to the corresponding pyrrolizines (23).

Another procedure for the synthesis of pyrrolizine derivatives utilizing substituted enamines with convenient functional groups is based on the Thorpe-Ziegler cyclization. This approach made it possible to synthesize a large number of pyrrolo[1,2-*a*]pyrroles and other heterocyclic systems containing the pyrrolizine moiety (86KGS564; 87KGS1616; 89KGS830; 91KGS19; 93MC160). For example, when treated with a base, exocyclic enamines in the pyrrolidine series containing an *N*-cyanomethyl group (24) give bicyclic compounds (25) in a smooth reaction (86KGS564; 87KGS1616).

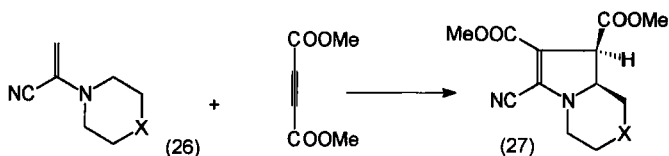


The Thorpe-Ziegler cyclization was also used in a new synthesis of hydroindoles according to Scheme 1 (93MC160). The utilization of  $\alpha$ -cyanoenamines has proven to be very advantageous. Thus, for example,



SCHEME 1

$\alpha$ -cyanoenamines (**26**) and dimethyl acetylenedicarboxylate heated at reflux in acetonitrile easily give annulated pyrrolines (**27**) (94T7075). The authors assume (94T7075) that the formation of **27** takes place via a [2 + 2]-cycloaddition followed by a new cyclization (83JA4775). Another type

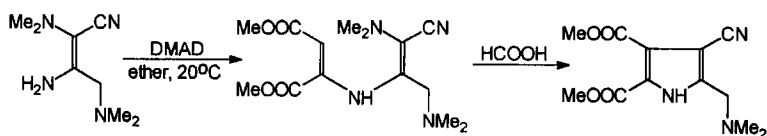


of reaction of cyanoenamines with dimethyl acetylenedicarboxylate takes place through an initial addition of the primary amino group of the enamine to the triple bond followed by a cyclization and elimination of dimethylamine (87JOC2427) (Scheme 2). Still another approach to 3-cyanopyrroles is based on electrophilic attack involving  $\alpha$ -cyanoenamines (92EUP491137) (Scheme 3).

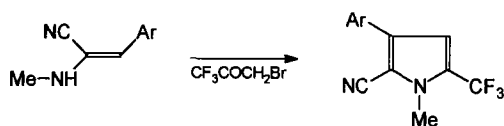
An entire series of heterocyclizations is based on  $\alpha$ -cyano- $\beta,\beta$ -bis(acetyl)enamines (84JOC4696). When treated with weak bases, compounds **28** give amidine intermediates (**29**), which undergo cyclization yielding five-membered ring derivatives (**30**). The subsequent hydrolysis of **30** affords high yields of pyrrolinones (**31**).

Considerable attention has been paid to the synthesis of indoles, enamines serving as the principal synthons to obtain new pyrrole-ring systems. The well-known Batcho-Leimgruber methodology (85OS214) was used to obtain indoles with methoxycarbonyl substituents in the benzene ring (95H1045, 95OPP576; 96JMC1806). A similar procedure has been used in the synthesis of pyrrolo[2,3-*b*]benzofurans (**32**) [90KFZ(3)34].

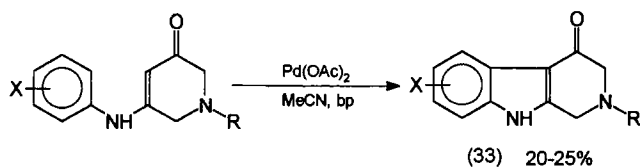
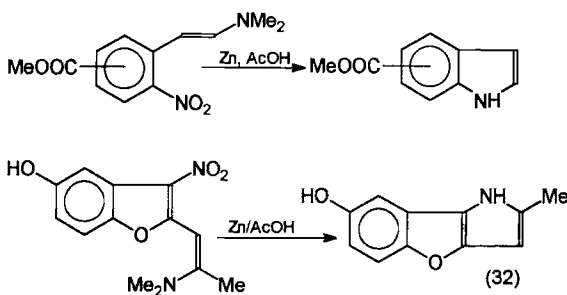
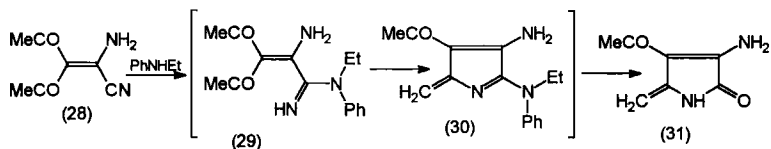
A different type of indole ring synthesis was accomplished via an intramolecular cyclization of enaminketones that proceeds through intermediate arylpalladium complexes (90H911).  $\beta$ -Hydrocarbolines (**33**) were obtained as the final products. Similar results were obtained in the photocyclization of enaminoesters (91TL6129) and enamino lactones (95H1939). Results obtained in the cyclization of *N*-arylenamines to indoles with



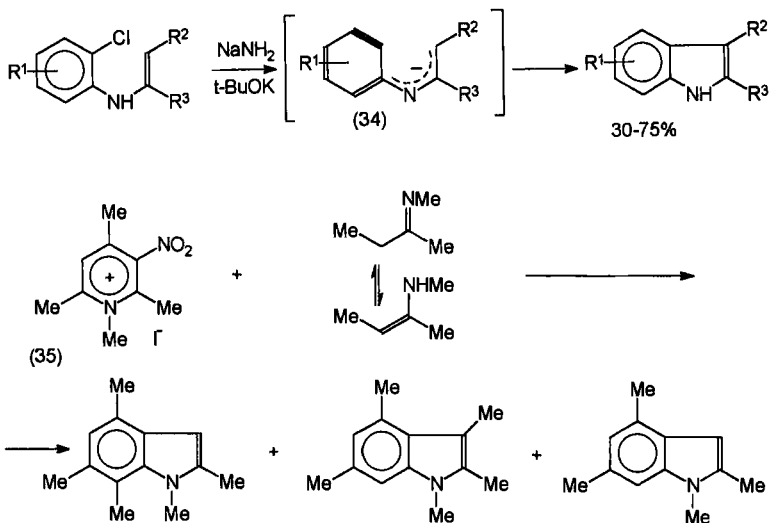
SCHEME 2



SCHEME 3

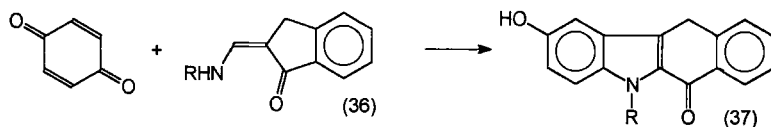


sodium amide/potassium *tert*-butoxide are analogous to those described earlier (90H911; 91T6129; 95H1939). Indole derivatives are obtained as the products (94T11903). However, the mechanism is different. An aryne anion (**34**) is the key intermediate and yields indole products. Indole ring formation from 3-nitrocollidinium cation **35** takes place in the presence of imines, which are in a tautomeric equilibrium with the corresponding enamines. The rate depends on the enamine and increases with its increasing equilibrium concentration (92KGS1187).

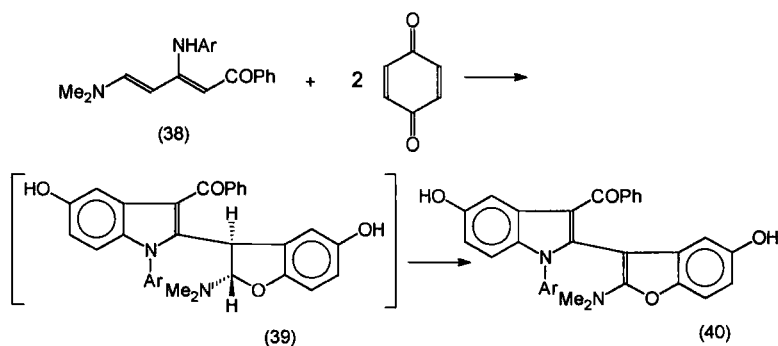


One of the most widely used synthetic approaches to 5-hydroxyindoles is the Nenitzescu reaction. A classical example is the interaction of *p*-benzoquinone and its derivatives with various enamines. In the present contribution, only the most recent papers devoted to the Nenitzescu reaction will be discussed because a detailed review on this topic has been published recently [93KFZ(6)37] and this topic has received considerable attention in one of the chapters in a monograph (94MI1). One study involves the reaction of benzoquinone with indane enamines (**36**) (94AP137) leading to 2-hydroxybenzo[*b*] carbazole derivatives (**37**).

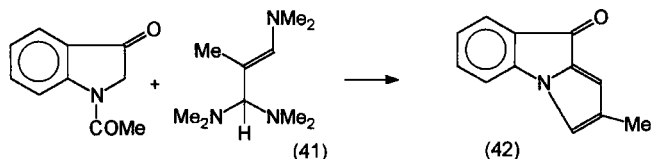
Condensation reactions of enaminoesters, enamino ketones, and enamino nitriles with benzo- and chloronaphthoquinones have been described (94JIC281). Utilization of diamines (**38**) as novel synthons in the Nenitzescu reaction has resulted in a new synthesis of 2-(3-benzofuryl)indoles (**40**) [95KFZ(9)47, 95MC69]. The pathway in the scheme leading to **40** has

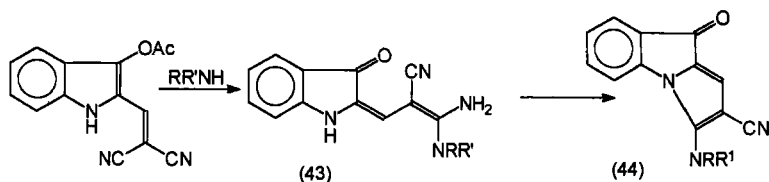


been confirmed by an independent synthesis [95KFZ(9)22, 95KFZ(12)3]. One of the interesting features of the reaction of dienediamines **38** with benzoquinone was the retention of the dimethylamino group in position 2 of the benzofuran ring in **40**. This, as a rule, is quite unusual in the Nenitzescu reaction, which normally takes place with cleavage of the amino fragment [93KFZ(6)37]. In the preceding case, 2,3-dehydrogenation takes place in the last step of the formation of **40**. The authors have attempted to explain this observation as due to the special stereochemical features of intermediate **39** [95KFZ(12)3], in which the dimethylamino group and the proton in position 3 are *s-syn* with respect to each other (according to molecular models).



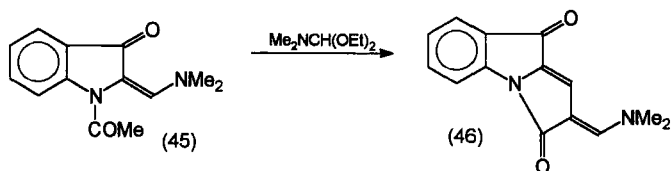
There are numerous additional studies based on the properties of enamines and the synthesis of the pyrrole ring. Thus, fusion of dienediamines formed by a reaction of amins of  $\alpha,\beta$ -unsaturated  $\beta$ -dimethylaminoaldehydes (**41**) with *N*-acetylindoxyl results in cyclization to pyrroloindoles (**42**) (87IZV821). Dienediamino derivatives of a different type (**43**) obtained from indoxyl are also transformed into pyrrolo[1,2-*a*]indoles (**44**) upon



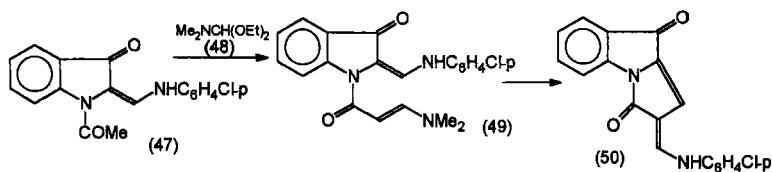


heating in acetic acid or acetic anhydride [95KFZ(9)22, 95KFZ(12)3]. The unusually facile noncatalytic addition of amines to the cyano group is said to be due to the intramolecular participation of the hydroxy group in position 3 of the indole ring [95KFZ(9)22].

Another interesting synthetic route to pyrrolo[1,2-*a*]indoles is based on *N*-acetylindoxyl (92MC59). The reaction of *N*-acetylindoxyl with the diethyl acetal of dimethylformamide yielded enaminoketone (45), which subsequently gave a tricyclic enaminoketone (46) in an unexpected reaction



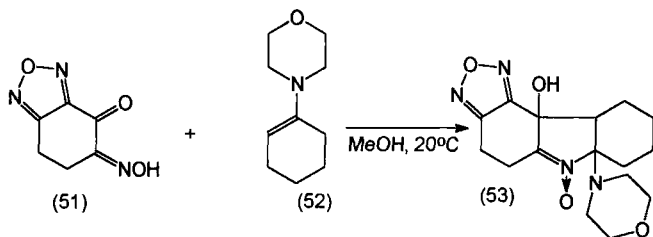
with  $\text{Me}_2\text{NCH}(\text{OEt})_2$ . To study the mechanism of this unusual process, the authors synthesized *N*-arylenaminoketone 47, which reacted with acetal 48 to give a bis-enamine (49), isolated pure. When heated in xylene, 49 undergoes a number of transformations due to the attack of the  $\alpha$ -position of one enamine fragment upon the  $\beta$ -position of the second enamine fragment with the formation of a mixture of 49 and 50 (according to TLC). Compound 46 undergoes transamination with *p*-chloroaniline and gives tricyclic 50 (92MC59). 1-Acetyl-2-formyl-3-acetoxyindole also gives an analogous reaction.



Other reactions involving the formation of the pyrrole ring include reactions of enamine anions with 1,2-dichloroethane or epichlorohydrin

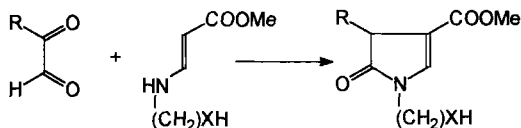
[87JCS(CC)775], reactions of benzotriazolylenamine anion with imines (95TL343), expansion of the aziridine ring (83BSB193), reaction of imines with enamines (84JOC2691), and bis-acylation of the isoquinoline-based enamines with oxalyl chloride (94KGS946).

Reaction of 4-oxo-5-hydroxyimino-4,5,6,7-tetrahydrofuranan (**51**) with the morpholine enamine of cyclohexanone (**52**) leads to oxadiazolo[3,4-c]carbazole (**53**) (94KGS199). Similar results were obtained with the corre-



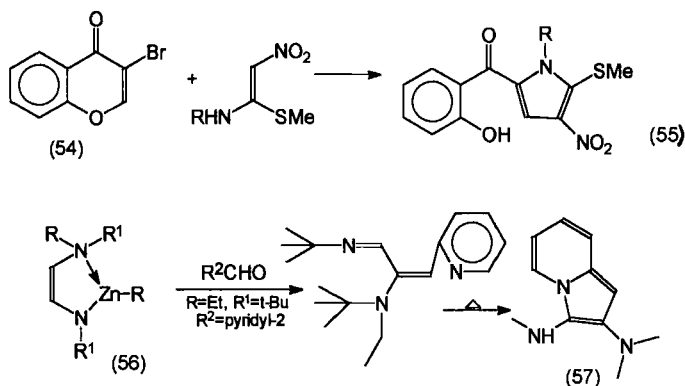
sponding benzofuroxan derivatives (94KGS199).  $\alpha$ -Diketones can also interact with enamines with formation of pyrrolinone derivatives (94T7849) (Scheme 4). Ring opening of the pyrone system takes place in the course of the reaction of 3-bromochromone (**54**) with ketene *S,N*-acetal and is followed by subsequent recyclization to a pyrrole ring (**55**) [95IJC(B)639]. Condensation of  $\alpha$ -aminozinc enamines (**56**) with aldehydes yields indolizines (**57**) in high yields (92TL7933). Pyrrole cyclization was observed in the reaction of silylenamines with phenacyl bromide (86CB257) followed by hydrolysis and interaction with a primary amine (Scheme 5).

Recently, several new contributions devoted to the synthesis of pyrrole derivatives from enamines have appeared. A new titanium-mediated approach to pyrroles from enaminoketones has been described (95JOC6637). Upon irradiation, cyclic enaminoketones are transformed to carbazole derivatives (96SC657). Pyrrole derivatives are also obtained by reaction of enaminothioamides with  $\alpha$ -bromoketones in the presence of a base. With *p*-toluenesulfonic acid as a catalyst, the course of the reaction changed and a 1,4-thiazepine derivative was obtained as the principal product (95JHC1679). Cyclic enaminonitriles can be used in a Thorpe-Ziegler reaction, leading to hydrogenated indole derivatives [96KFZ(6)47]. 3-



SCHEME 4



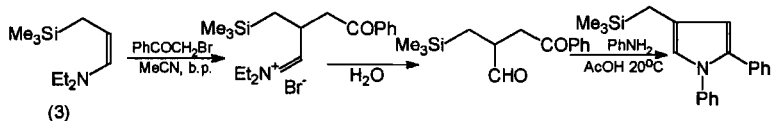


Nitropyrrole derivatives are obtained by reaction of nitroenamines with propargyl bromide [95JCS(P1)1725].

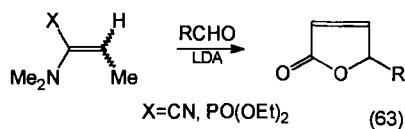
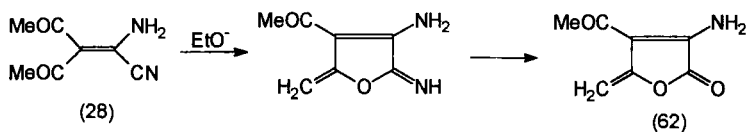
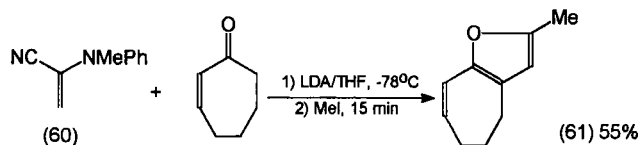
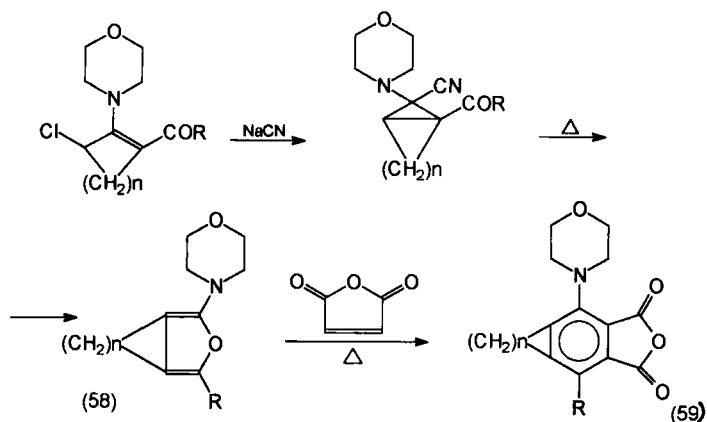
## B. SYNTHESIS OF FURAN AND THIOPHENE DERIVATIVES

In the preceding section, the interaction between enaminoamides containing a chlorine atom in the  $\beta$ -position and various nucleophiles results in the formation of a pyrrole ring. As a continuation, the interaction of chloroenamines with cyanide anion, with interfacial catalysis, was investigated. This reaction leads to aminocyclopropane derivatives, which when heated in boiling formic acid give aminofurans (58) and in the presence of maleic anhydride afford the corresponding condensed phthalic anhydrides (59) (90T8103).

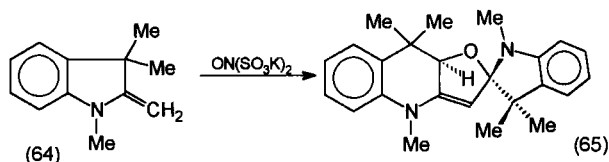
Cyanoenamines are used for the synthesis of the furan ring. For example, the anion of 3-cycloheptenone gives the Michael addition with  $\alpha$ -cyanoenamine (60); subsequent methylation results in the closure of the furan ring and formation of a furan-containing bicyclic derivative (61) (91S133).  $\alpha$ -Acetyl- $\beta$ -amino- $\beta$ -cyanovinyl methyl ketone (28) was converted into a 2-furanone derivative (62) in the presence of the ethoxide anion (84JOC4696). Five-membered ring lactones (63) are formed by reaction of cyanoenamine anions or phosphorus-containing enamines with aldehydes (84T733).

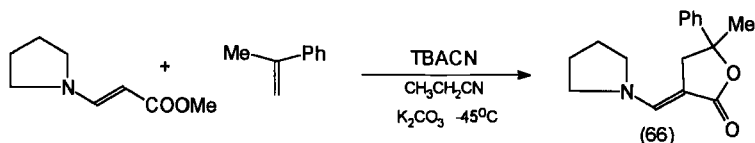


SCHEME 5

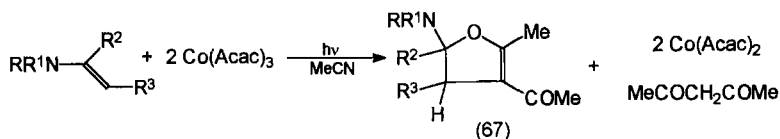


Oxidation of 1,3,3-trimethyl-2-methylenindolinone (**64**) with potassium nitrodisulfonate leads to a five-ring *spiro* product (**65**) (83CB1309). Enaminoesters react with olefins in the presence of tetrabutylammonium cerium(IV) nitrate (TBACN) as the oxidizing agent; the overall process proceeds via a cation radical and affords an enaminolactone (**66**)

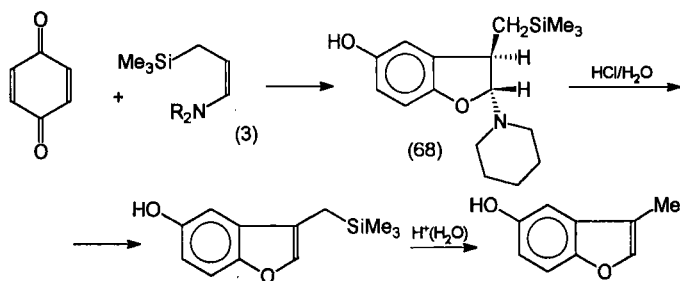




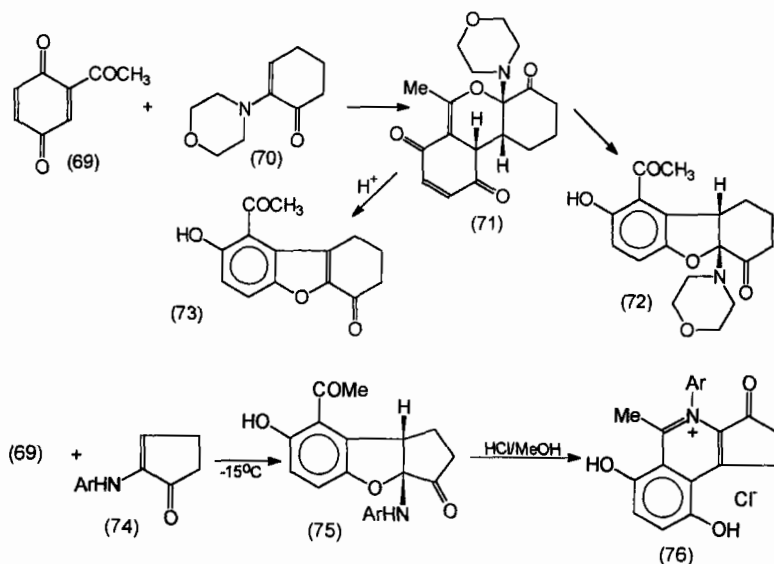
(92CL2099). Dihydrofurans (**67**) were synthesized by a photochemical reaction of enamines with metallic complexes of diketones (83CL1499). As an example, the reaction with cobalt(III) acetylacetonate is presented.



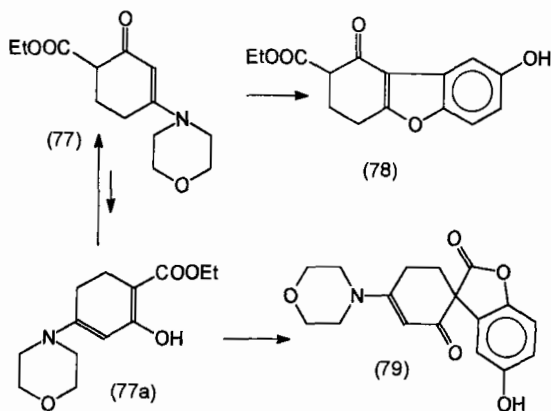
Syntheses of various substituted benzofurans are based on the Nenitzescu reaction, as summarized in previous reviews [93KFZ(6)37; 94MI1]. Thus, silylenamines **3** undergo a facile condensation with *p*-benzoquinone and give the 2,3-dihydro derivatives of 5-hydroxybenzofurans (**68**). When refluxed in 15% hydrochloric acid, **68** reacted with elimination of the corresponding amine and hydrolytic cleavage of the silyl fragment (86CB257).



Reaction of 2-acetyl-*p*-benzoquinone (**69**) with 2-morpholino-2-cyclohexen-1-one (**70**) gives benzo[*c*][4*H*]chromene-4,7,10-trione (**71**), which undergoes a rearrangement with the formation of dihydrobenzofuran (**72**); acid hydrolysis affords a dihydro derivative of dibenzofuran (**73**) (93JPR345). Compound **69** reacts with five-membered ring *N*-arylenaminone **74** giving **75**, an analog of **72**, which then undergoes an acid-catalyzed rearrangement to an isoquinolinium salt (**76**). Annulated benzofurans were also obtained in reactions of enaminones of type **74** with 2,5-dichloro-*p*-benzoquinone (93AP415).

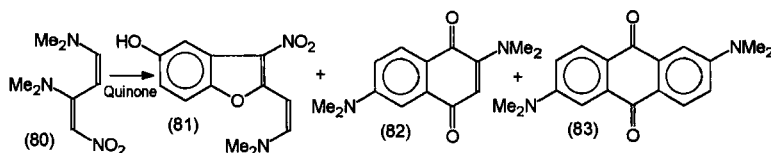


In the case of enaminoketone (77) and *p*-benzoquinone, there are two parallel reactions: in the  $\beta$ -position of the enamine 77 and in the  $\delta$ -position of the tautomeric dienamine 77a [93MC40; 94KFZ(2)36]. The first pathway (common in the Nenitzescu reaction) gives a dibenzofuran derivative (78), the second affords an unusual product—a *spiro*[benzofuran-3,1'-cyclohexene] derivative (79). The likely pathways are indicated. The

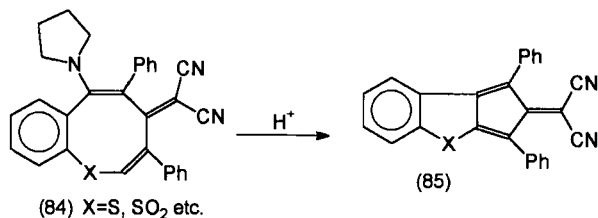


synthesis of benzofurans based on reaction of indolylenamines with *p*-benzoquinone was discussed (95MC69). The reaction of *p*-benzoquinone with nitrodienediamine 80 follows two pathways, one of them leading to a

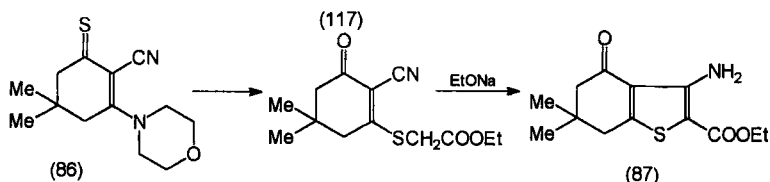
benzofuran derivative **81** (Nenitzescu reaction) and the second to naphtho- and anthraquinone derivatives **82** and **83**, respectively (1,4-cycloaddition) [95KFZ(9)44, 95MC68].

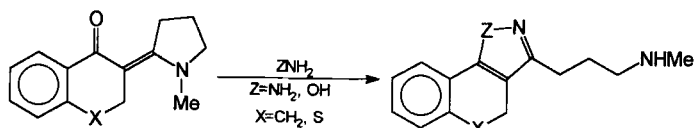


In studies of the stereochemical aspects of the Nenitzescu reaction it was established that the direction of benzofuran synthesis in reactions of enamines with *p*-benzoquinone depends on the size and electron-withdrawing properties of the substituents in the starting materials (97T177). Among the few studies devoted to the formation of thiophene derivatives and based on reactions involving enamines is the acid-catalyzed deamination of eight-membered ring enamines (**84**). Fulvene-type compounds (**85**) are obtained (82CL847).



Thiophene ring closure (product **87**) based on the Thorpe–Ziegler reaction utilizes 2-cyano-3-ethoxycarbonylmethylthio-5,5-dimethyl-2-cyclohexen-1-one obtained from enaminothione **86** (93MC160). Thiolactams give thiophene derivatives in the Eschenmoser reaction. This reaction depends on the size of the lactam ring. Cyclization to thiophenes takes place with six- and seven-membered rings but not with five-membered ring lactams (96H63). The reaction of  $\alpha$ -mercaptoenaminodinitriles with *N*-cyanochloroacetamidine yields thiophene derivatives (96T1011). Closure



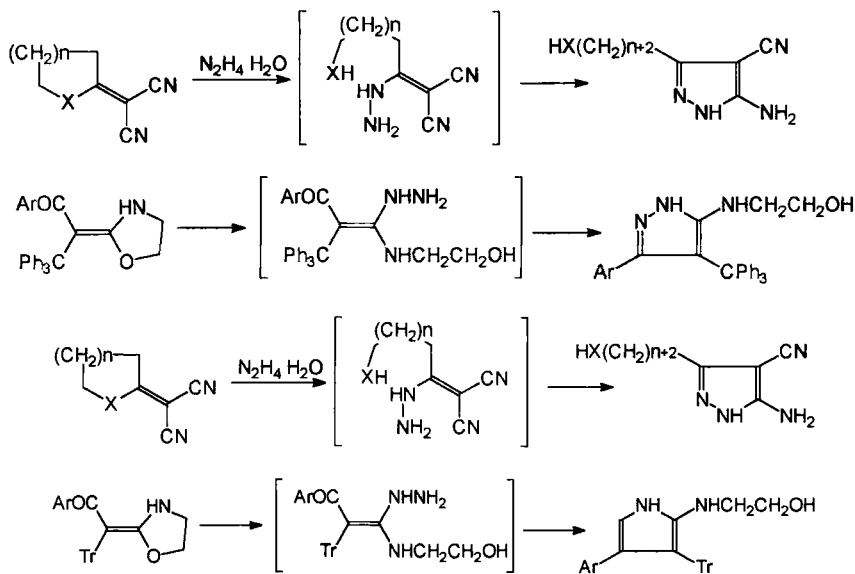


SCHEME 6

of the thiophene ring from enamidines-*N*-(3-aminothioacryloyl)lactam imines has been described (93JPR639). In the same publication, the formation of thiazole derivatives is discussed.

### C. SYNTHESIS OF THE AZOLES

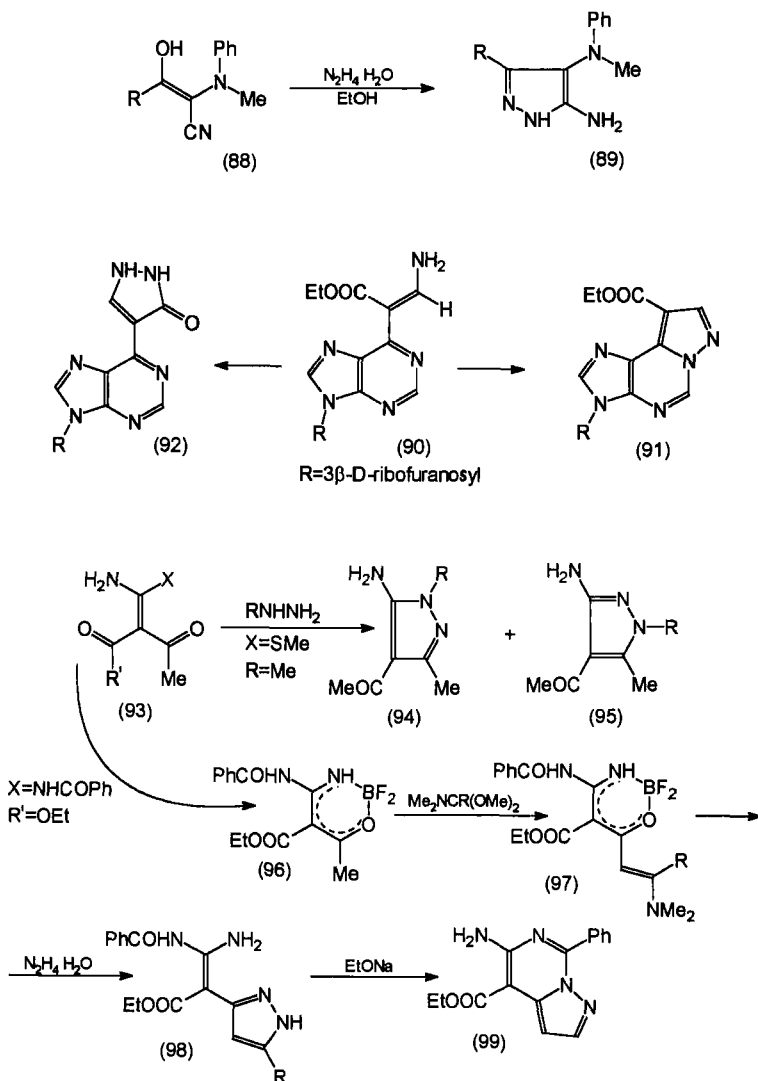
A common approach to the synthesis of pyrazole-based heterocycles using enamines as synthons is the interaction of enaminocarbonyl compounds or enaminonitriles with hydrazine or with substituted hydrazines to obtain pyrazole derivatives (89CP51; 96JHC1243) and condensed pyrazoles and isoxazoles [83IJC(B)1083] (Scheme 6). An analogous principle, based on the ring opening of a saturated enamine-based heterocycle and accompanied by the formation of a pyrazole ring in the presence of hydrazine hydrate, has been discussed (91JHC1257). The oxazolidine ring is opened similarly (95SC3603) (Scheme 7).



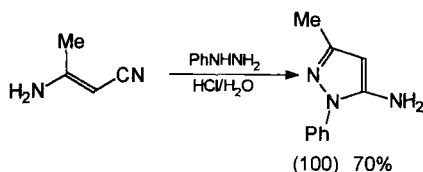
SCHEME 7

Reaction of  $\alpha$ -cyanoenamines (**88**) containing a hydroxy group in the  $\beta$ -position with hydrazine hydrate gives aminopyrazoles (**89**) (85S794). Enaminoesters in the purine series (**90**) also react with hydrazine hydrate via two different pathways with the formation of pyrazolopurines (**91**) and 1-(4-pyrazolyl)purines (**92**), respectively (94JOC1525).

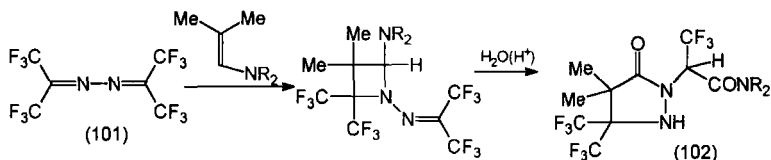
*N,S*- and *N,N*-Acetals of dicarbonyl substituted ketenes (**93**) also serve as



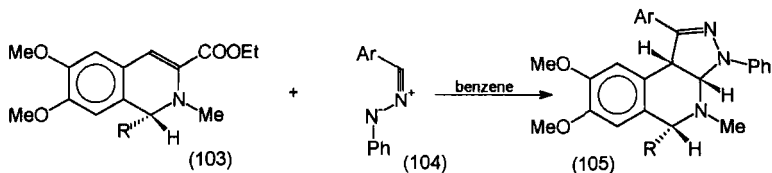
starting materials in the synthesis of pyrazole derivatives (**94**, **95**) and as reactants in the reaction with substituted hydrazines (93IZV1429). The same starting materials serve as substrates in a preliminary chelate synthesis with the formation of intermediates (**96**) with an activated methylene group. This approach was used to synthesize new enamine chelates (**97**) and substituted pyrazoles (**98**, **99**) (84CPB2496). The reaction of  $\beta$ -enaminonitriles with hydrazine derivatives leads to aminopyrazoles (**100**) in a smooth process (93JOC6155).



Cycloaddition reactions represent another route to pyrazoles from enamines. For example, azine (**101**) and enamines react via a  $[2 + 2]$ -cycloaddition with the formation of azetidines that undergo acid hydrolysis



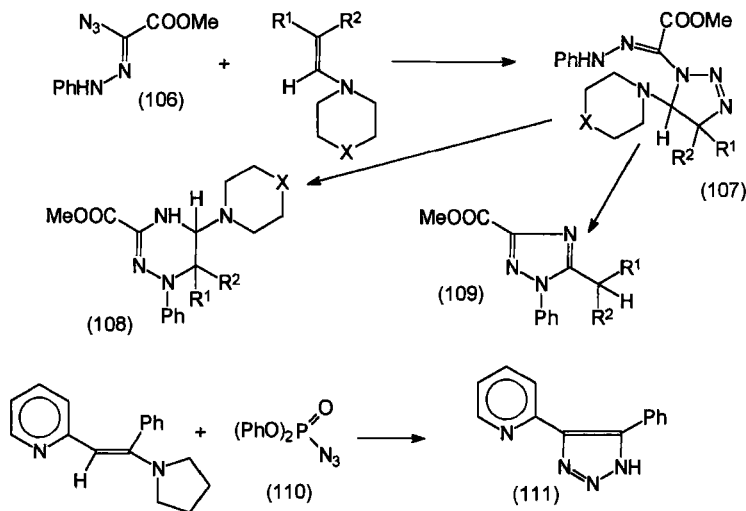
to tetrahydropyrazolones (**102**) in low yields (82LA853). Cycloaddition of diarylnitrilimines (**104**) to enamines in the isoquinoline series (**103**) leads to pyrazoloisoquinolines (**105**) (92CJC802). The synthesis of pyrazole derivatives based on "push-pull" enamines and using hydrazine hydrate has been described (97KGS89, 97KGS329).



Cycloaddition reactions can also be used for the synthesis of various triazole derivatives. Thus, for example, the reaction of azidohydrazone (**106**) with enamines includes a 1,3-dipolar cycloaddition of the azido group to the



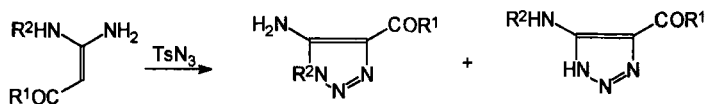
enamine double bond in the first stage of the overall process. The reaction results in the formation of unstable  $\Delta^2$ -1,2,3-triazolines (**107**), which can subsequently react by several different pathways, one of which is a loss of nitrogen leading to **108**. The degradation of **107** by evolution of nitrogen and a hydride shift affords triazoles (**109**) [84JCS(P1)1427; 95OPP603]. A similar 1,3-dipolar cycloaddition of phenyl azide to silylenamines with the formation of 1,2,3-triazole derivatives has been described (86CB257). Diphenyl phosphoazidate (**110**) used in an analogous process yielded triazole (**111**) (84CPB2496). 1,2,3-Triazole derivatives are also formed during



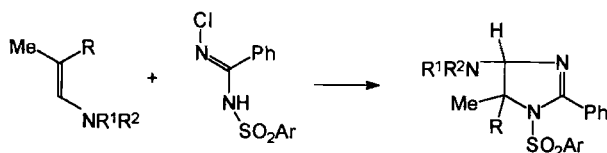
interaction of phenyl or tosyl azides with enediamines (86S1010; 90IZV1392) (Scheme 8). Several recent studies describe a diazo transfer from diazocarbonyl compounds to enaminketones and enaminoesters (93JOC7079; 94T6723). These reactions yielded triazole and fused pyrazole derivatives.

Few publications are devoted to the synthesis of imidazole derivatives; the reaction between *N*-chloro-*N*-benzenesulfonylamidines with enamines shown in Scheme 9 serves as an example (87T4785).

A "reverse" variant of this reaction is the interaction of enamines with amidines in the presence of an equimolar amount of bromine. Bromine at-

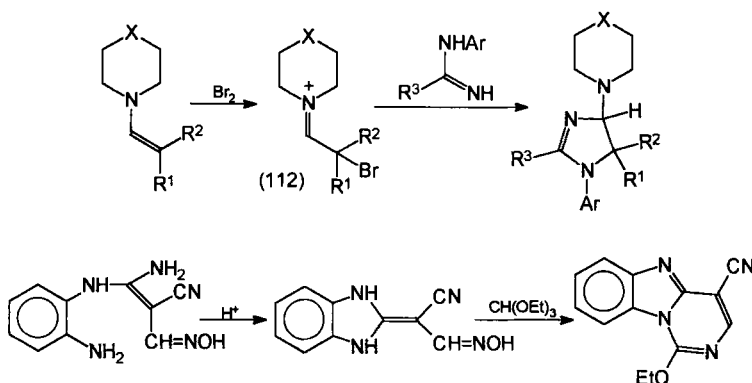


SCHEME 8

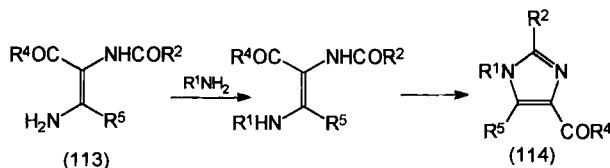


SCHEME 9

tacks the  $\beta$ -position of the enamine, and this results in the formation of a bromonium salt (**112**), which then reacts with the nucleophilic nitrogen atom of the amidine through the  $\alpha$ -position of the salt **112**; this is followed by cyclization in the presence of triethylamine (83S940). The synthesis of pyrimidobenzimidazoles from enamionitriles and some reactions of these tricyclic compounds have been discussed (86JHC1829; 95JHC851). The synthesis of naphthimidazole derivatives has been described (96JHC1217).

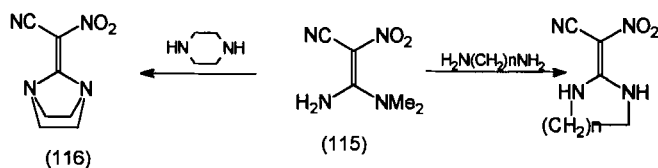


2-Acylaminoenaminoketones (**113**) are readily accessible by reduction of isoxazoles; in the presence of bases they give imidazoles (**114**) in a facile

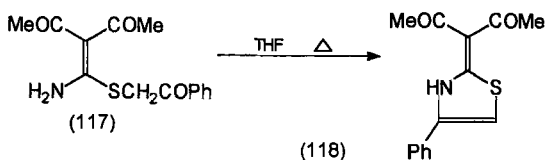


reaction (87JOC2714). Highly polarized enamines of type **115** easily react with ethylene- and propylenediamines and give hydro derivatives of imidazole or pyrimidine (96KGS811). The reaction of **115** with piperazine

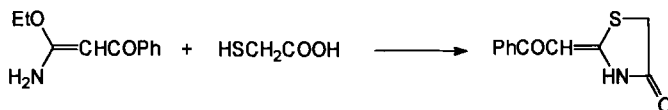
gives the bicyclic derivative **116** with an imidazolidine moiety. Syntheses of oxazolo[3,2-*a*]pyridines based on the reaction of enamines with unsaturated ketones were described (91T6503; 93T10079), and the stereochemistry and regiochemistry of the products were investigated. The regioselectivity of the process depends on the structure of the ketone and specifically on the presence or absence of an electron-withdrawing substituent in its  $\beta$ -position.



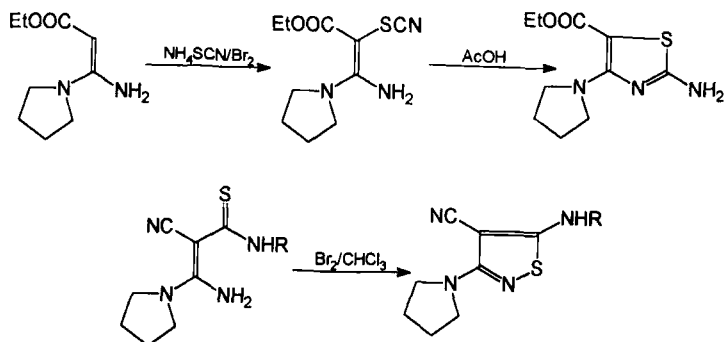
A number of studies have been devoted to the synthesis of thiazoles and related cyclic systems. Sulfur-containing starting materials and enamines are used. Thus, the reaction of  $\alpha$ -alkoxyenaminoketones with mercaptoacetic acid (ester) smoothly gives thiazoles (89S775) (Scheme 10). Substituted  $\alpha$ -mercaptoenamines clearly are intermediates; *N,S*-diacylketene acetals (**117**) undergo a facile cyclization with the formation of thiazoles (**118**)



when heated in tetrahydrofuran (93IZV1938). A successful modification of the synthesis of substituted thiazoles described the reaction of enaminonitriles or enaminoesters with sodium or ammonium thiocyanate in the presence of bromine as an efficient route to aminothiazoles (93S199) (Scheme 11). A similar procedure utilizing dithiocyanogen (from ammonium thiocyanate and elemental bromine) has been described for enaminoketones and enaminoesters lacking the second amine moiety in the  $\alpha$ -position



SCHEME 10



SCHEME 11

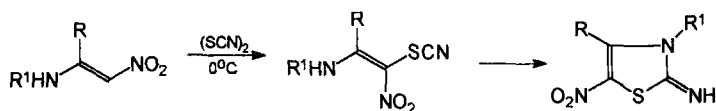
(92JPR711). Also, nitroenamines can be used as the starting materials for the synthesis of thiazoles (85JOC1547) (Scheme 12).

A synthesis of isoxazoles is based on ring-opening of the thiazolidine ring in the respective enamines in the presence of hydroxylamine (95SC3219) (Scheme 13). A conversion of *N*-acylglycines (through the corresponding  $\alpha$ -acylamino enaminesters) (95JHC1563) to 1,2,4-oxadiazole-3-carboxylates has been published.

#### D. OTHER SULFUR- AND PHOSPHORUS-CONTAINING FIVE-MEMBERED RINGS

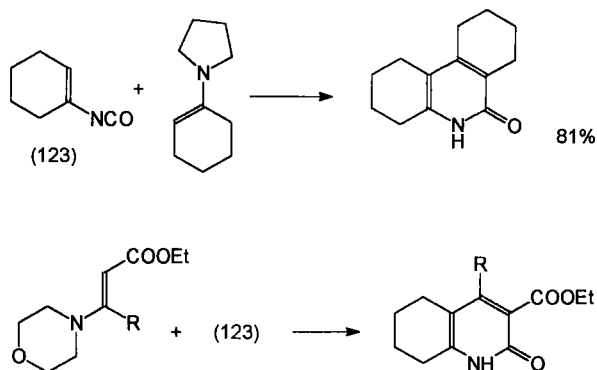
Other heterocyclic systems that do not belong to the structural types discussed in the preceding sections will now be considered. Silylenamines react with carbon disulfide to form a trithione derivative (**119**) (86CB257). Enaminoketones and carbon disulfide react in the same fashion (91JHC1245).

Finally, interaction of  $\beta$ -enamino- $\lambda^5$ -phosphanes (**120**) with dimethyl acetylenedicarboxylate and the subsequent treatment of intermediate **121** with butyllithium gives the  $\lambda^5$ -phosphole derivatives **122** [89JCS(P1)2273].



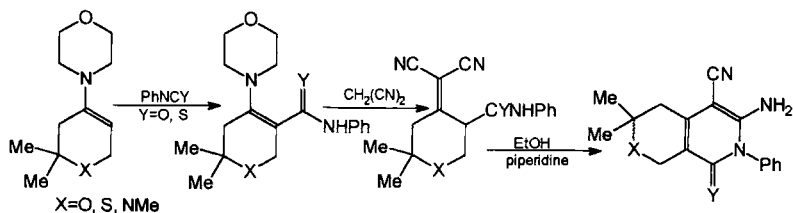
SCHEME 12



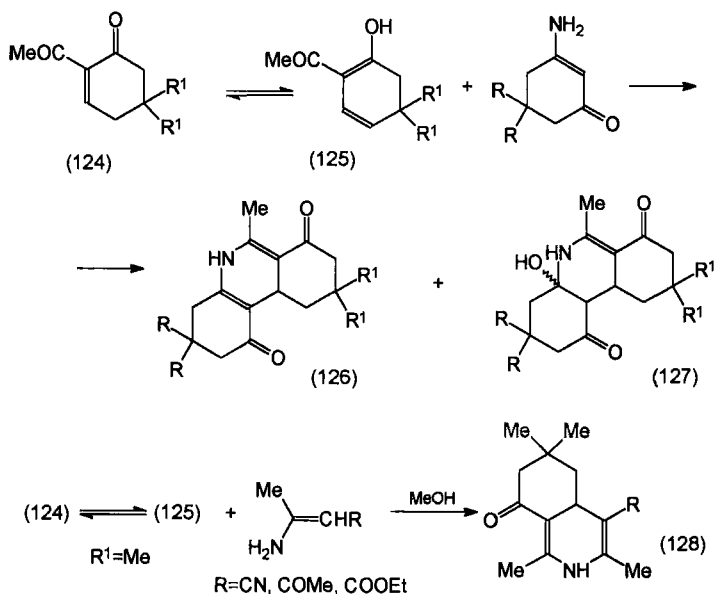


were used as the electrophilic reagents to introduce an amidic or thioamidic substituent, respectively, into the  $\beta$ -position of the corresponding enamines. This approach formed the basis for the synthesis of the pyridine ring and the synthesis of pyrano- and thiopyrano[3,4-c]pyridine and 2,7-naphthyridine (87AKZ587) (Scheme 14).

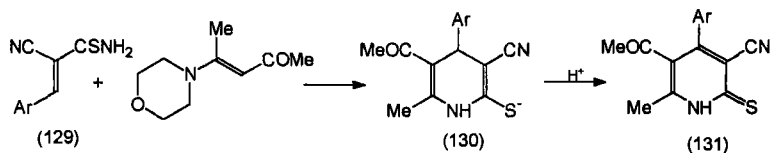
A very important topic devoted to the formation of heterocyclic rings from enamines deals with their use in the synthesis of 1,4-dihydropyridines (for review articles on dihydropyridines, see 88H269; 92KGS435; 93KGS579). Enamines based on cyclic diketones react with derivatives of 2-acetyl-2-cyclohexen-1-one (**124**), which are in a tautomeric equilibrium with unsaturated hydroxyketones (72IZV407), and fused 1,4-dihydropyridine (**126**) and 1,2,3,4-tetrahydropyridine derivatives (**127**) (two isomers) (90KGS66; 92KGS631). An analogous synthesis of aryl-substituted 1,4-dihydropyridines has been described (92KGS631). Reaction of acyclic enaminoesters and enamino ketones with an equilibrium mixture of **124** and **125** affords 1,4-dihydropyridines (**128**). The reaction of cyclic enamino ketones with activated olefins is closely related to this work (94PHA365). Unsaturated thioamides (**129**) easily react with  $\beta$ -diketones



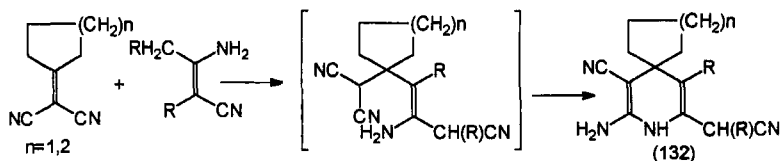
SCHEME 14

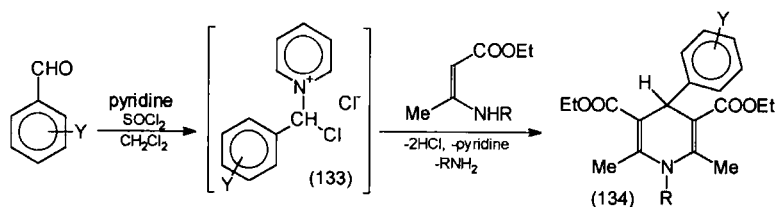


or the corresponding enaminoketones with the formation of 1,4-dihydropyridinium salts (**130**). Their treatment with an acid and subsequent oxidation leads to 2-pyridinethiones (**131**) (85ZOR683). Similar studies have been described (82MI1; 85MI1; 92MI2).



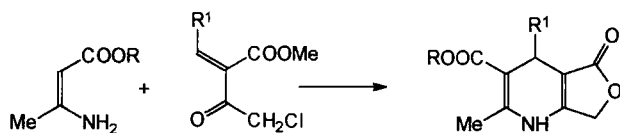
Enaminonitriles and cycloalkylidenemalonodinitriles gave *spiro* cyclic compounds (**132**) containing a 1,4-dihydropyridine moiety (90MI1). A number of *N*-substituted Hantzsch 1,4-dihydropyridines (**134**) were obtained under mild and neutral conditions from *N*-substituted enaminocarbonyl compounds and aldehydes, activated by interaction with thionyl chloride and pyridines (92SC3291, 92T1263).





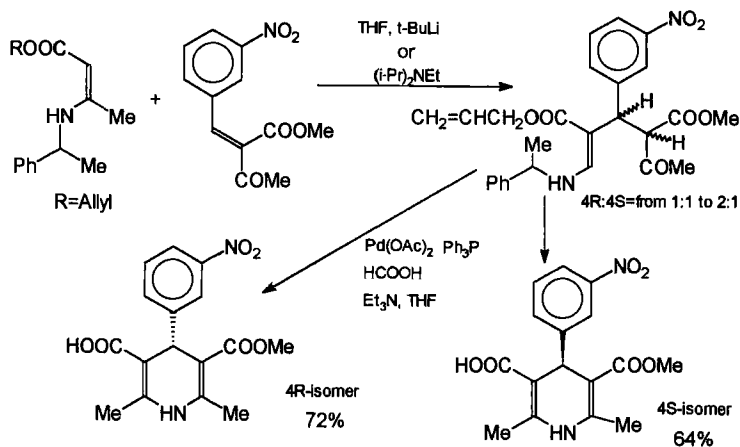
Yields of dihydropyridines (**134**) are determined by the electronic characteristics of the N-substituents because the first step of the process involves an electrophilic attack of an *N*-(1-chloroalkyl)pyridinium chloride (**133**) upon the  $\beta$ -position of the respective enamine, and strongly electron-withdrawing properties of the substituent R prevent this step from taking place. Another important factor is the possible protonation of the amine being formed in the reaction. If the amine basicity is low, it can react with the salt **133** and thus prevent the formation of **134**. As mentioned, 1,3-dicarbonyl compounds easily react with enaminoesters. When these compounds contain additional functional groups as substituents, other processes become possible. The formation of a lactone shown in Scheme 15 serves as an example (95KGS966). One synthesis of optically active 1,4-dihydropyridines [94H(39)591] is based on the separation of intermediates containing an (*R*)-1-phenylethylamino group. This study can be represented as shown in Scheme 16.

A rather complex scheme, which ultimately leads to a tetracyclic compound **137** containing a 1,4-dihydropyridine ring, is based on the condensation of ninhydrin (**135**) with enaminoesters (**136**) (95JHC33). An unexpected formation of 1,4-dihydropyridines fused to an indole ring was observed with 3-arylmino-1-acetylindoles (**138**). These derivatives exhibit well-pronounced enamine-like properties. Electrophilic attack of the Vilsmaier reagent on these compounds takes place in position 2 of the indole ring. The reaction, in a two-step process, leads to a 1,2-dihydro-8-carboline derivative (**139**), which upon alkylation in the presence of potassium carbonate and ketones yields tricyclic compounds (**139**) [95MC107; 96KFZ(9)29]. A new approach to the synthesis of dihydropyridines utilized the  $\alpha$ -azaallyl anion (**140**) as the synthon for cyclization [85JCS(CC)466].

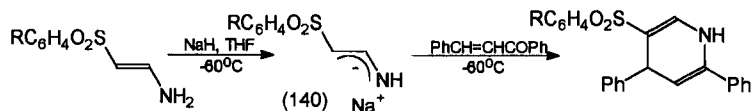
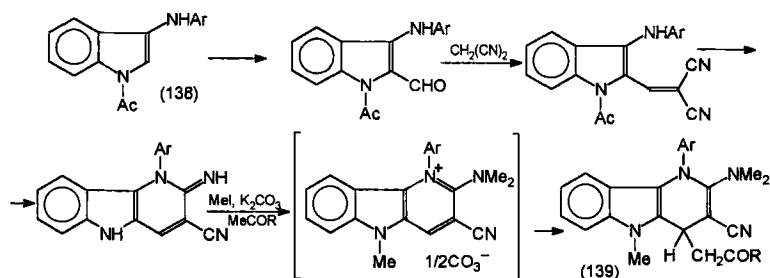
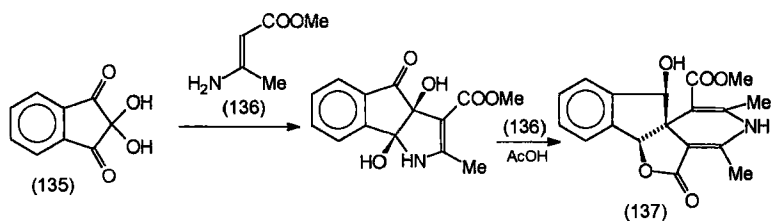


SCHEME 15

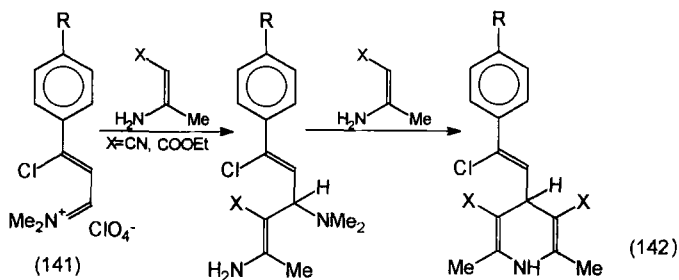




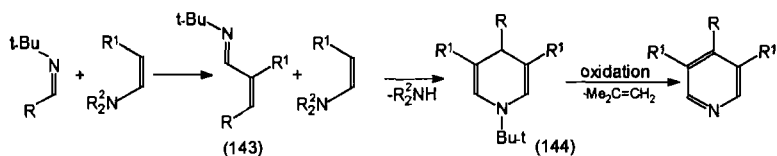
SCHEME 16



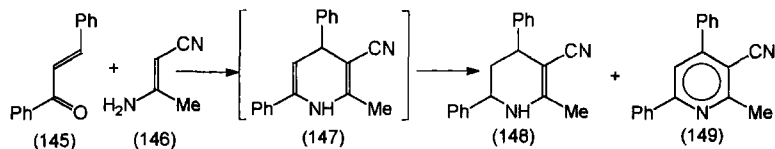
Studies of reactions of 3-chloro-2-propenyliminium salts (**141**) with enamionitriles and enaminoesters (59CCC2385; 72ZC417; 76JPR705) established that the cationic center in **141** attacks the  $\beta$ -position of enamines, and this is followed by a cyclization to 1,4-dihydropyridines (**142**) with



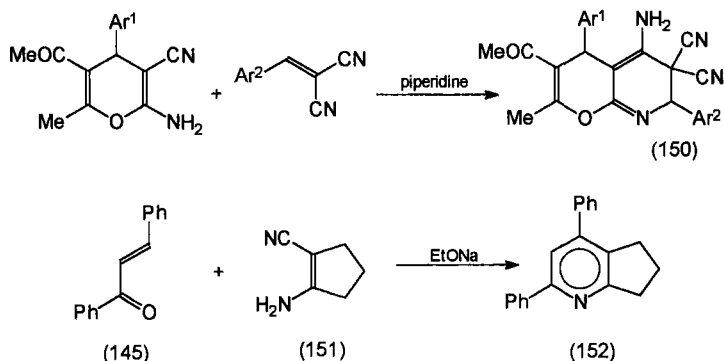
the participation of a second molecule of the enamine [87AP(B)520]. 1,4-Dihydropyridines are also formed in the reaction between enamines and imines. The proposed scheme envisions an initial [2 + 2]-cycloaddition followed by the formation of an azadiene (**143**), its 1,4-cycloaddition to the enamine, and subsequent oxidation of the intermediate 1,4-dihydropyridines, (which very often can be isolated, albeit in low yields) to pyridines (**144**)



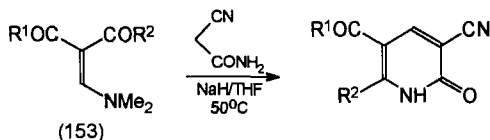
(84JOC2691). Analogously, in the reaction of chalcone (**145**) with the enamionitrile **146**, the intermediate dihydropyridine (**147**) can be detected only in trace amounts because it undergoes disproportionation with the formation of tetrahydropyridine (**148**) and pyridine derivatives (**149**) (92JOC7352). Fused 5,6-dihydropyridines (**150**) were obtained from cyclic



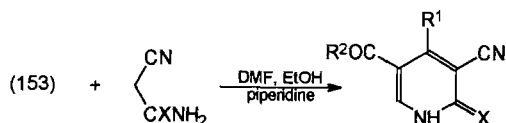
enamines in the pyran series and arylidenemalononitriles (91CCC2175). Compound **145** and 1-amino-2-cyanocyclopentene (**151**) give the 2,4-diphenyl-6,7-dihydropyridine derivative (**152**) in a smooth reaction (92JOC7352).



Numerous papers have been devoted to the synthesis of various derivatives of 2-pyridone, 4-pyridone, and aminopyridines based on enamines, di-enamines, dienediamines, and related compounds. For example, enamino-diketones (**153**) can react with cyanoacetamide in tetrahydrofuran in the presence of sodium hydride with the formation of a substituted 3-cyano-2-

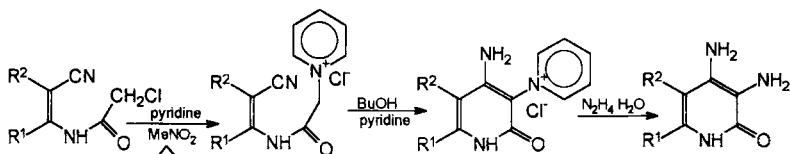


pyridone (**154**) (90JHC511). Under analogous conditions (95S557), **153** also reacted with cyanothioacetamide. However, with piperidine in place of sodium hydride, the process proceeds by a different pathway. Whereas in the first case attack takes place on the methylene group of a 1,3-diketone, in the latter case, because of the lower proton-accepting characteristics



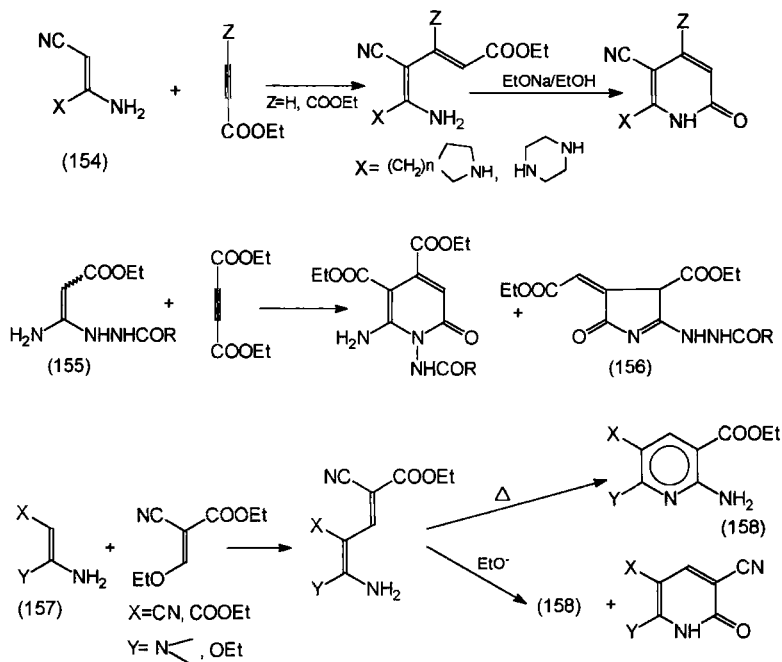
of the base, the reaction involves transamination (95S923). An interesting method of synthesis of 2-pyridones has been proposed (95LA787) (Scheme 17).

Enaminonitriles (**154**) easily react with esters of acetylenedicarboxylic acid or propiolic acid. The first step is an electrophilic attack of the reactant on the  $\beta$ -position of the enamine, and this is followed by cyclization with



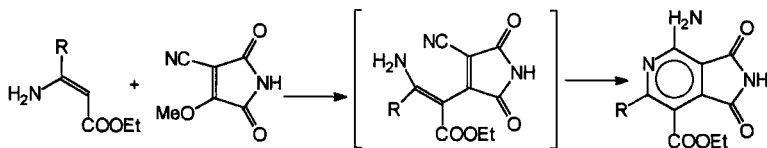
SCHEME 17

the formation of 2-pyridone derivatives (92S371). Another closely related reaction is that of *N*<sup>1</sup>-acylacetamidrazones (**155**) with acetylenedicarboxylate. In ethanol and in the presence of acetic acid, substituted pyrrolones (**156**) are obtained along with 2-pyridone derivatives (95H1479). Also, activated enamines (**157**) undergo condensation in the  $\beta$ -position with alkyl-



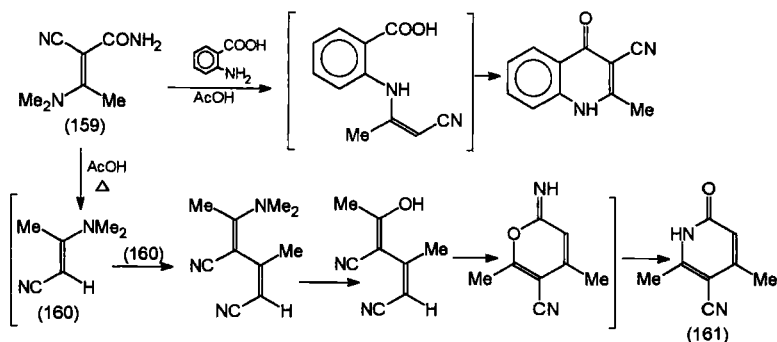
denecyanoacetic esters. The resulting aminodienes undergo cyclization to 2-pyridone and 2-aminopyridine derivatives (e.g., **158**) upon heating or in the presence of a base (90JHC1143). The initial attack at the position with the highest electron density of the enamines also seems to take place in their reaction with 3-methoxy-4-cyanomaleimide [84JPR(B)594] (Scheme 18).

A similar approach to the synthesis of the pyridine ring, using different



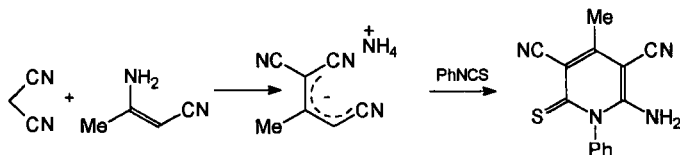
SCHEME 18

starting enamines and electron-deficient olefins, has been used in a number of studies (89S775; 95JHC543). An unexpected result was obtained when  $\alpha$ -cyano- $\beta$ -dimethylaminomethacrylamide (**159**) was heated in acetic acid. According to the authors (86KGS84), an elimination of cyanic acid is followed by an attack of the  $\alpha$ -position of one molecule of enamionitrile **160** being formed upon the  $\beta$ -position of the second molecule of **160**. Cyanopyridone (**161**) is the product. Heating in the presence of anthranilic acid leads to transamination and formation of 2-methyl-3-cyano-4-quinolone

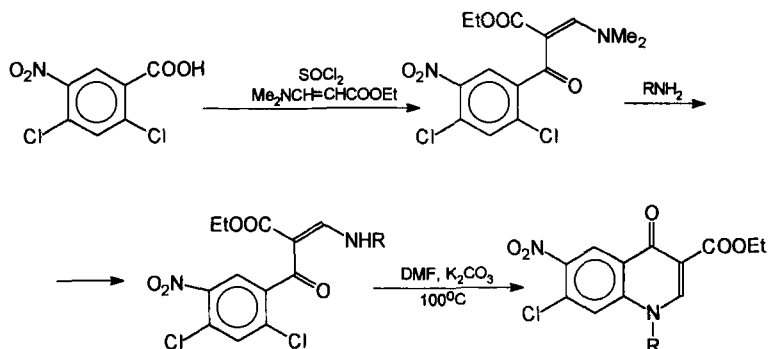


(86KGS84).  $\beta$ -Cyanoenamines interact with malonodinitrile followed by a reaction with phenyl isothiocyanate leading to 2-pyridone and 2-pyridinethione derivatives (95H2195) (Scheme 19).

Enamine-based synthetic procedures for the preparation of 4-quinolones are well known and have been described in review articles (89MI1; 91PHA485) and recent papers [87KFZ1249; 94H(38)2091, 94IZV299;



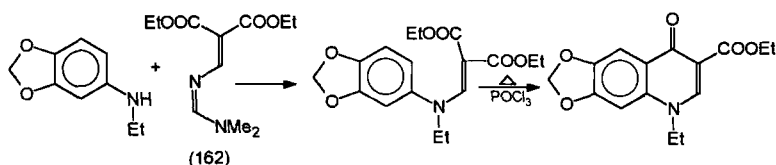
SCHEME 19



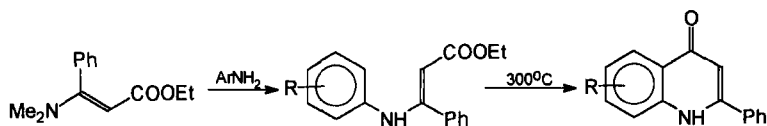
SCHEME 20

95JMC973]. The reaction of dichloronitrobenzoyl chloride with ethyl dimethylaminoacrylate gave an enamino dicarbonyl compound, which upon treatment with amines undergoes transamination and substitution and gives an ester of a substituted quinolonecarboxylic acid (95JMC973) (Scheme 20). Another approach to 4-quinolone derivatives was demonstrated in Toda *et al.* [94H(38)2091], in which the initial transamination is coupled with thermal cyclization (Scheme 21).

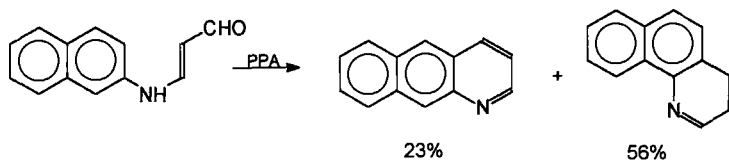
Enamidines (**162**) are new synthons for the synthesis of quinolonecar-



boxylic acids (87KFZ1249). Cyclizations accompanied by condensation of the carbonyl substituent in the side chain were described (95H2221, 95H2459) (Scheme 22). Aza-annulation using secondary enamines and acryloyl chloride as the reactants is based on the initial *N*-acylation



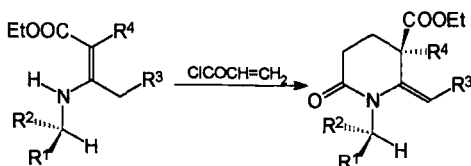
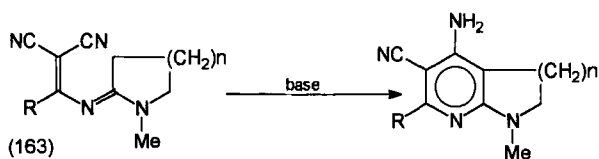
SCHEME 21



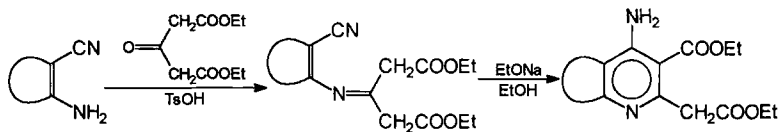
SCHEME 22

of enamine derivatives followed by cyclization [93TL8197; 94JA6201, 94KFZ(1)49]. The annulation process is highly diastereoselective. The dependence of annulation on temperature, solvent, and the structure of the acrylic reactant has been investigated (94JA6201) (Scheme 23).

A series of investigations has been carried out concerning the synthesis of substituted enamines with a functional group capable of participation in a new condensation reaction leading to the formation of the pyridine ring. There are a number of possible variations of the condensation reaction depending on the structure of the starting reagents. Thus, condensation of primary enamionitriles with the acetylenedicarboxylate ester results in situations in which the cyano group is the active group involved in the cyclization and formation of the pyridine ring (95M333) (Scheme 24). An analogous situation arises when ketones react with enaminoaldehydes. In this case, the cyclization in the last reaction step occurs with the participation of the formyl group (86KGS1649). A similar approach with enamidines (**163**) has been used (92JHC1067).



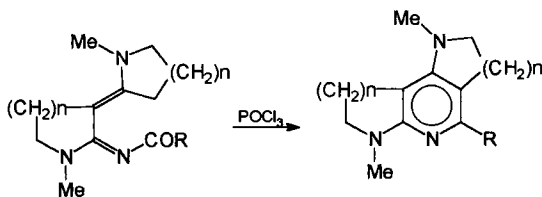
SCHEME 23



SCHEME 24

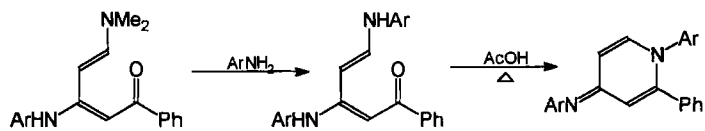
The substituent active in the cyclization can be separated from the enamine moiety. This approach has been adopted for the synthesis of fused pyridines (90TL131) (Scheme 25). The reaction is much easier in the case of six-membered ring azacycloalkanes; see a review (82RCR207). Another type of an intramolecular cyclization with the participation of the NH group has been reported (95MC24) (Scheme 26). One of the cyclization reactions discussed in this paper involves the ethoxycarbonyl group in the  $\beta$ -position of an enamine (Scheme 27). Numerous studies devoted to this type of cyclization have been published (82KGS68; 83KGS1279; 84KGS799, 84KGS1252; 85KGS646, 85KGS929; 95JHC291; 96JMC1112), including several reviews (84RCR651; 92KGS762, 92T4985). Functional groups capable of participating in these cyclizations include keto, nitrile, alkoxy-carbonyl, and carbamoyl groups. Diverse syntheses of the pyridine ring are represented in the structures that follow (82KGS68; 84KGS1252; 85KGS929) (Scheme 28). The dimethylaminomethylene moiety can also be used as a "hidden" formyl group for cyclization in the *o*-position of aromatic and heteroaromatic rings (90SC469, 95JHC1293) (Scheme 29).

One of the synthetic methods leading to 2-pyridones is based on enaminoamides and leads to basic enaminoacylamidines. They can be transformed directly into 2-pyridones or into 4-pyrimidinones, which can undergo recyclization leading to substituted 2-pyridones (76KGS1509; 77KGS1106; 80KGS416, 80KGS1120; 81KGS269; 82KGS518). This ap-

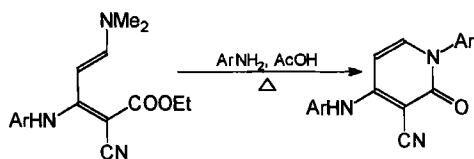


SCHEME 25

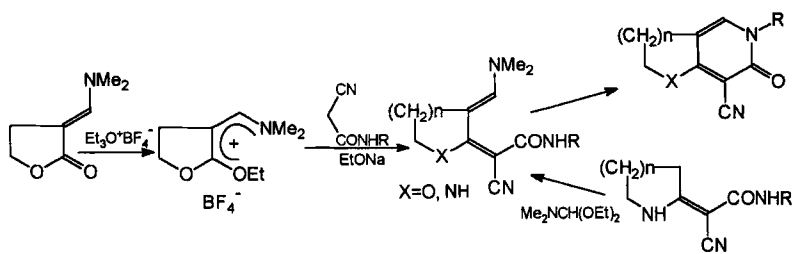




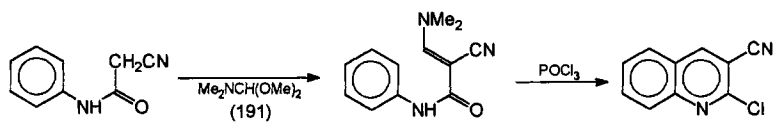
SCHEME 26



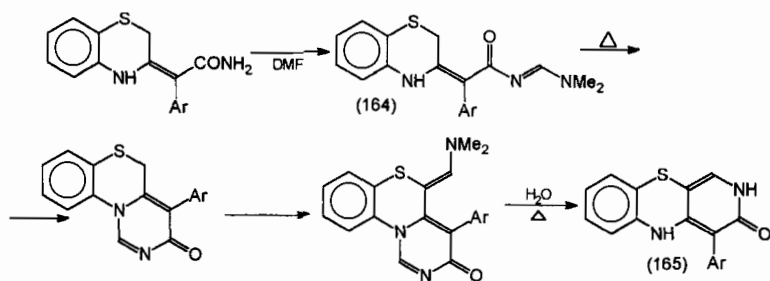
SCHEME 27



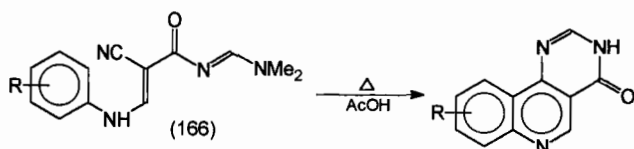
SCHEME 28



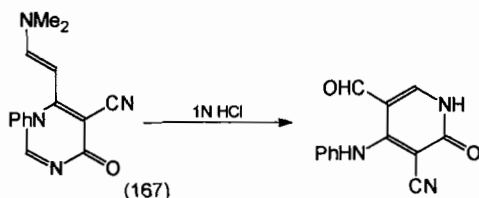
SCHEME 29



proach was used to synthesize a large number of substituted 2-pyridones and various condensed pyridines (84KGS1287; 85KGS646; 86KGS1118; 87JOC1366). The synthesis of a large group of derivatives of pyrimido[3,4-c]- and pyrido[3,4-b]benzothiazine (165) illustrates this methodology (87JOC1366). Enaminoacylamidines (166) have been used to prepare other tricyclic compounds with the pyridine moiety (84KGS538; 88KGS88). The

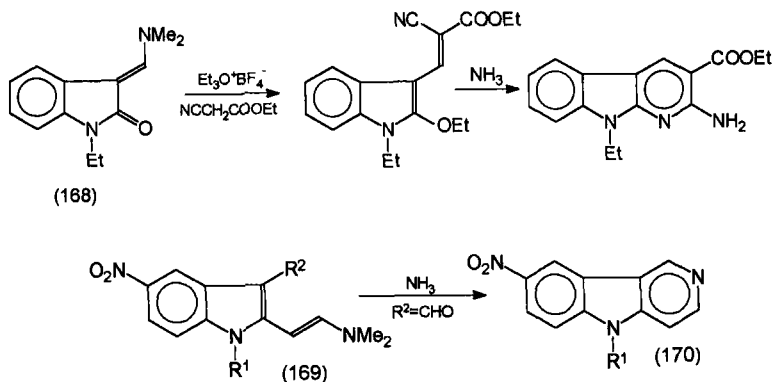


same scheme (87JOC1366) shows that one of the key steps in the synthesis of the pyridine ring is recyclization of a pyrimidinone into a pyridine; this usually proceeds smoothly in an alkaline medium (81KGS269; 82KGS518). Hydrolysis of heteroarylenamines of this type (167) takes place in an acidic medium, allowing the synthesis of 2-pyridones with a formyl group in position 5 (86KGS1118).



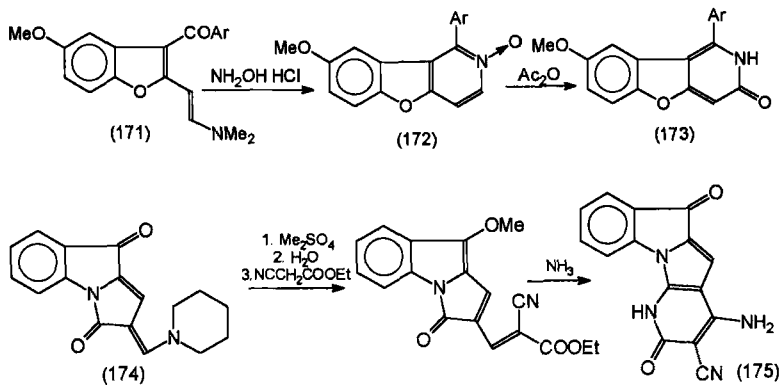
Various heteroarylenamines were starting materials in the synthesis of pyridine derivatives. For example, 3-dimethylaminomethylenoxyindole derivatives (168) were used in the preparation of  $\alpha$ -carboline (95MC226).

Indolylenamines (169) undergo a facile transformation into  $\gamma$ -carboline



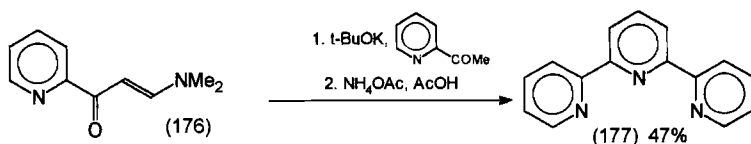
(170) with different structures depending on the substituent in position 3 of the indole ring (90KGS1483; 92KGS502).

Treatment of benzofurylenamines (171) with hydroxylamine affords *N*-oxides of pyrido[4,3-*b*]benzofurans (172) [93KFZ(4)41; 93MC146; 96KFZ(3)54], which subsequently give the corresponding fused pyridones (173). An enamine in the indoxyl series (174) was also utilized in the synthesis of fused pyridines (175) [93MC238; 94KGS(8)919].

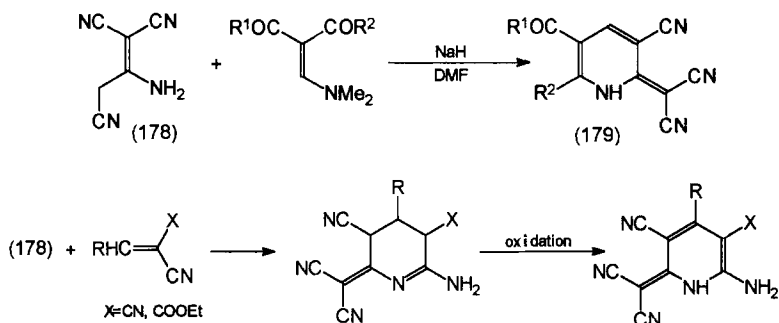


Dimethylaminomethylene derivatives, usually obtained by condensation of the dimethyl acetal or diethyl acetal of dimethylformamide with an active methylene group, can react with carbanions. This results in various heterocyclization reactions including formation of the pyridine ring (91TL1999; 95S557). Thus, enamine 176 and the 2-acetylpyridone anion give 2,2':6',2''-terpyridine (177) (91TL1999).

Malonodinitrile dimer (178) reacts with enamino dicarbonyl compounds

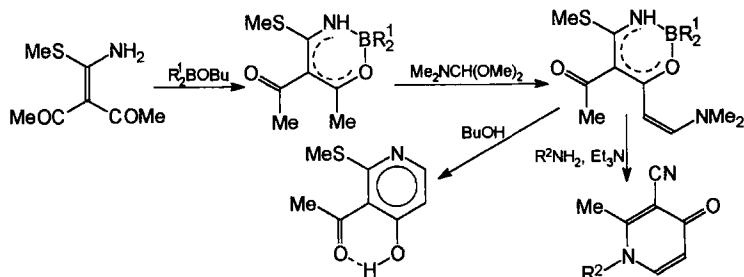


and gives 2-(dicyanomethylene)pyridines (**179**) (95SS557). Enamine **178** can interact with methylenemalonodinitriles and related compounds in the presence of sodium ethoxide (95JHC29).

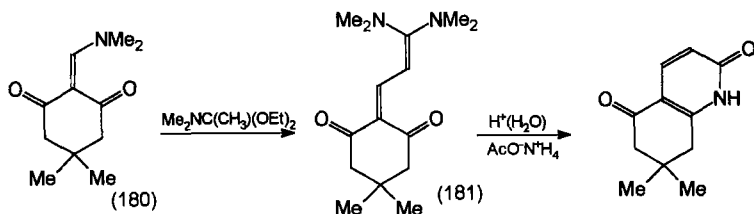


A recent efficient approach toward the synthesis of pyridine derivatives employs boron-containing chelates obtained from enamino carbonyl compounds (92IZV1455, 94IZV1322, 94IZV1342). A synthesis based on an *N,S*-acetal of diacetylketene serves as an example (94IZV1322) (Scheme 30).

Quite unusual processes were observed in the reactions of dimethylaminomethylenedicarbonyl compounds **180** with the diethyl acetal of *N,N*-dimethylacetamide. In these cases, the latter compound reacts as an *O,N*-acetal and the reaction results in the formation of new dienediamino dicarbonyl compounds **181**, which in turn serve as the starting materials for the synthesis of pyridine derivatives (86KGS127; 87KGS423, 87KGS1470).

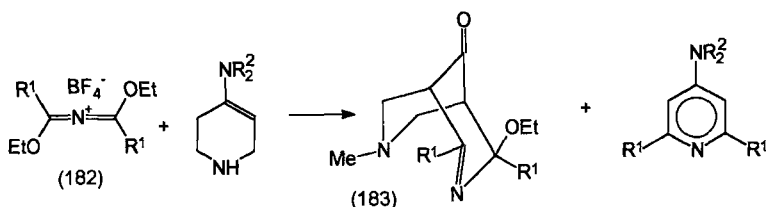


SCHEME 30

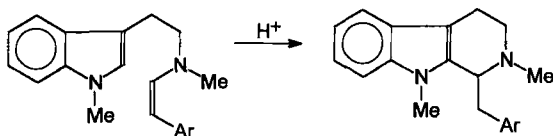


Some synthetic approaches to the pyridine ring are based on intramolecular cyclization with the participation of the  $\alpha$ -position of the enamine moiety. Cyclizations of this type were carried out with enamines obtained from tryptamine (a variation of the Pictet–Spengler reaction) (83AJC833; 92LA1063; 93TL7673). The authors assume (92LA1063) that iminium salts are the key intermediates (Scheme 31). An attack on the  $\alpha$ -position of the iminium salts also has been postulated in the intermolecular interaction of enamines with nitromethylisoxazoles (91H1913) (Scheme 32).

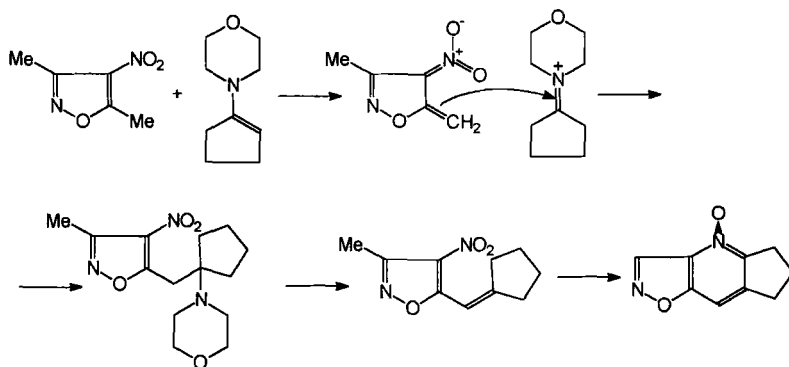
Iminium salts (**182**) were starting materials in reactions with enamines (93CB133; 94CB1437), which proceed by two different pathways: with the formation of bicyclic ketones (**183**) and with the formation of substituted pyridines. The authors assume that the reaction takes place by a double electrophilic attack of the salt (**182**) in the  $\beta,\beta$ -positions of the enamine and the resulting immonium cations undergo a *retro*-Mannich type of reaction with the opening of one of the piperidine rings.



Among the papers directed toward the synthesis of pyridine-like compounds and based on enamines, the following are depicted in the scheme: synthesis of fused isoquinolines (86MI1), preparation of 4-pyridones by



SCHEME 31

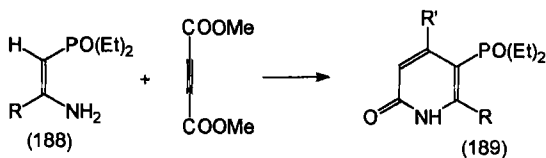
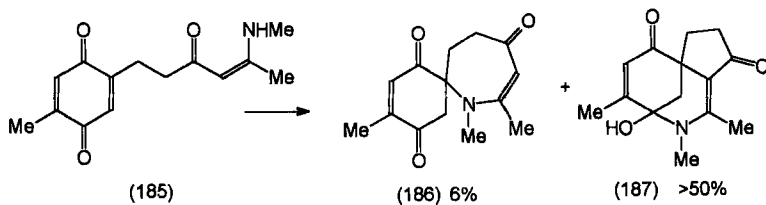
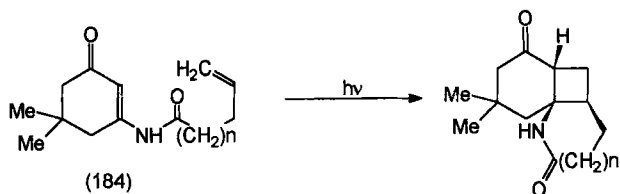
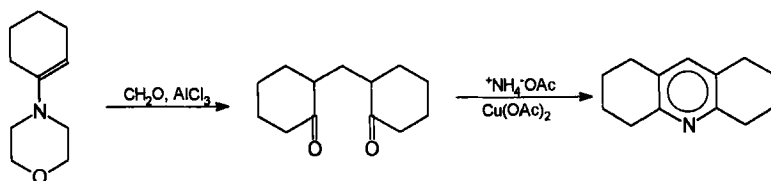
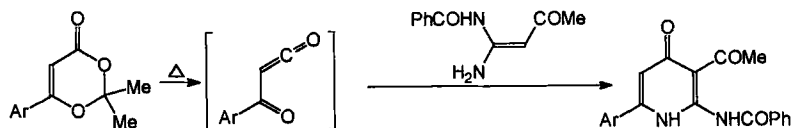
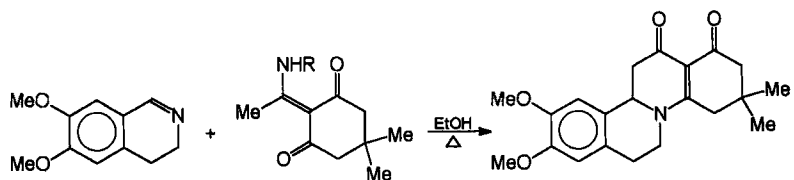


SCHEME 32

interaction of aroylketenes with enediamines (93IZV235), reaction of enamines with formaldehyde followed by ring closure (92MI3), and [2 + 2]-photocyclization of the enaminketone **184** accompanied by a simultaneous piperidine ring closure (92TL7933). Cyclization of quinonylenamines (**185**) gives *spiro* derivatives (**186**) and tricyclic products (94AP143).

The synthesis of 5-phosphonyl-2(1*H*)-pyridones (**189**) from  $\beta$ -enaminophosphonates (**188**) is presented (95H1915). Numerous further studies have been devoted to the synthesis of pyridine derivatives from enamines. The reaction of indanedione enamines with acrylonitrile derivatives leads to annulated 1,4-dihydropyridines (95MI1). Closure of the pyridine ring with the formation of pyrido[2,3-*g*]indoles by cyclization of the corresponding enaminoesters has been described (97KGS69). Ring closure of cyclic 2-arylaminomethylene-1,3-diones with the formation of condensed pyridines has been carried out (96JHC905). 4-Dimethylaminovinyl-3-cyanoquinoline derivatives undergo cyclization to the corresponding benzo-2,7-naphthyridones (96LA115). Cyclization of two pyridine rings to pyrido[3,2-*g*]quinoline derivatives is based on enamino esters (96H1621). Trimethylaluminum-promoted cyclization of cyanamines can be used for a versatile synthesis of substituted pyrazolo[3,4-*b*]pyridines (96SC981). Enaminonitriles serve as the starting materials for the 3-cyanopyridines (95PJC371, 95T1575).

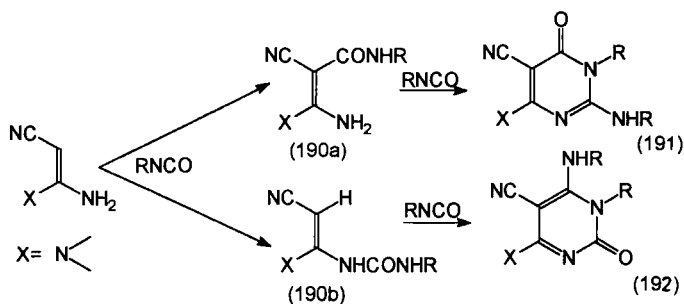
Interaction of substituted dienediamines with ethylenediamine yields imidazo[3,2-*a*]pyridine derivatives (95JHC477). 3-Arylaminoindoles, with distinct enamine properties, are the starting materials for the synthesis of indolo[3,2-*b*]quinoline derivatives [96KFZ(7)42].  $\alpha$ -Carboline derivatives can be obtained from enamine-based 3-dimethylamino-2-indolinones [96KFZ(9)35, 96KFZ(10)32]. The synthesis and transformation of enamines based on the pyrido[1,2-*a*]pyrazine ring system into imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine derivatives have been reported



(96JHC639). Closure of the pyridine ring based on enamine derivatives has been described (96JHC1041, 96JHC1303, 96JHC1407).

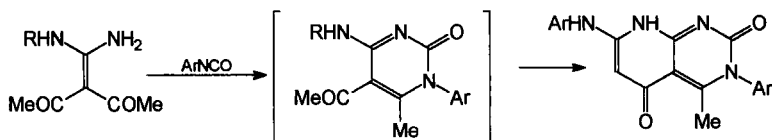
## B. CYCLIZATION REACTIONS LEADING TO PYRIMIDINES

The synthesis of the pyrimidine ring represents a well-studied group of heterocyclization reactions based on enamines. One of the important approaches involves the reaction of enamines with assorted isocyanates and isothiocyanates. Thus, a reaction of enaminonitriles with benzyl isocyanate or phenyl isocyanate gives C- and N-adducts (**190a** and **190b**, respectively) or their mixtures, which are transformed in a single step into 4-pyrimidinone (**191**) and 2-pyrimidinone (**192**) derivatives (94JHC329). The



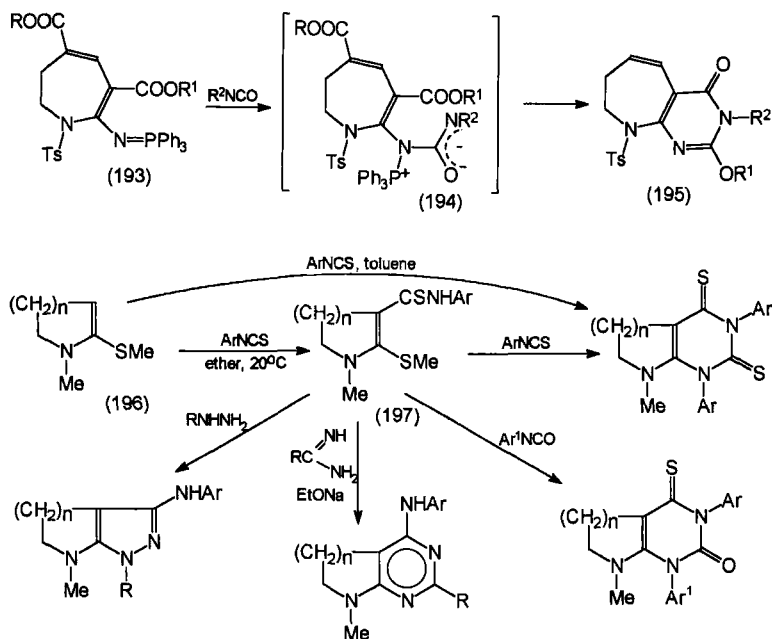
reaction of aryl isocyanates with  $\beta,\beta$ -disubstituted enamines takes place in an analogous fashion, with the formation of *N*-carbamido derivatives, and then can proceed further with a closure of a pyridine ring (90KGS1286) (Scheme 33).

Iminophosphorines (**193**) (representing the phosphorus-containing derivatives of enaminoesters) react with isocyanates with the initial formation of a zwitterionic intermediate (**194**), which is then transformed into 4-pyrimidinone **195** (90LA901). Aryl isothiocyanates react with cyclic enamines (**196**) by electrophilic substitution to give pyrimidinethiones (83S225). Intermediate **197** affords fused aminopyrimidines with amidines; aminopyrazoles are the final products with hydrazines (83S226). Aryl isothio-

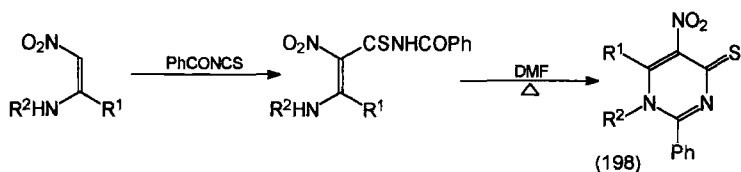


SCHEME 33



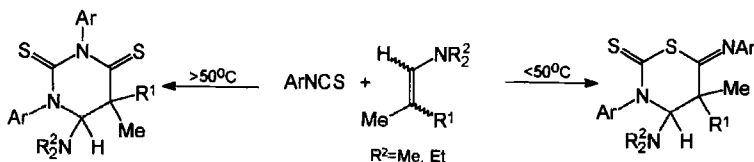


cyanates react with enamines (depending on the temperature) with the formation of hydrogenated pyrimidines and 1,3-thiazines (83CB55) (Scheme 34). Benzoyl isothiocyanate reacts with nitroenamines on the  $\beta$ -carbon atom; the resulting  $\beta$ -nitro- $\beta$ -(*N*-benzyl)thioamides undergo cyclization to nitrothiopyrimidines (**198**) upon heating (86BCJ3871).



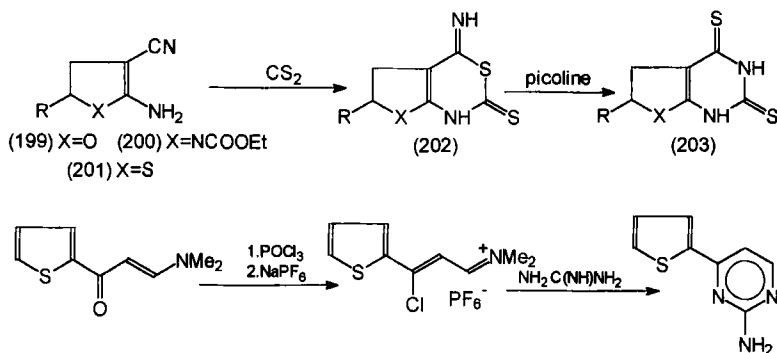
Benzyl isothiocyanates react analogously with other classes of enamino ketones including those without any additional active substituents (81CCC2696),  $\alpha$ -ethoxyenaminoketones (1,3-oxazine-4-thione derivatives are formed along with pyrimidines), and ketene acetals of acylketenes (93IZV1932). Another approach to the pyrimidine ring utilizes enamines and aminoheterocycles as starting materials (81JHC1287; 95H507) as illustrated (81JHC1287) (Scheme 35). However, enamionitriles (81JHC1287) and enamino ketones (95H507) react by transamination followed by cyclization.

Even the more complex enamines, such as the esters of  $\alpha$ -(2,2,-diethoxy-



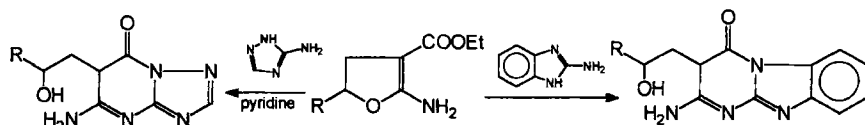
SCHEME 34

carbonylvinyl)amino- $\beta$ -dimethylaminoacrylic acid, react with aminoheterocycles in an analogous fashion (95JHC921). Enamines (**199**) and their aza (**200**) and thia (**201**) analogs react with carbon disulfide with the formation of 1,3-thiazines (**202**), which upon heating rearrange into 2,4-pyrimidinedithiones (**203**) [93JCR(S)302]. Treatment of vinylogous iminium salts with guanidine leads to pyrimidines. Various enaminketones react with "amidine components" in an analogous fashion (93JHC1517, 93JHC1653).

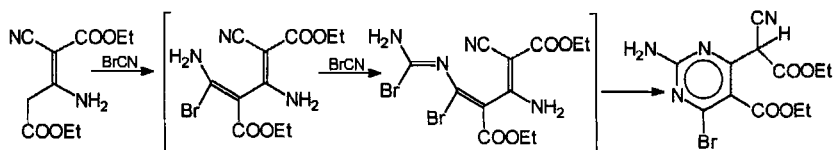


Enamine **204** reacts with cyanogen bromide with an unexpected result: an aminocyanopyrimidine derivative **206** is the product. The reaction proceeds by the addition to the primary amino group with formation of compound **205** followed by cyclization and replacement of the trichloromethyl group by cyano group [85JCS(P1)1499].

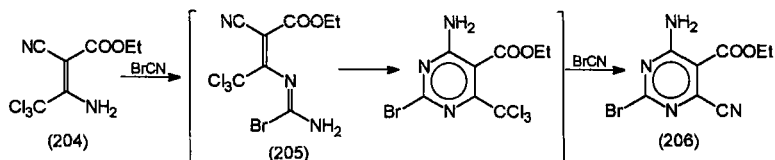
In the absence of a trichloromethyl group in the enamine structure, the process follows a different route. Thus, the cyanoacetic ester dimer reacts with cyanogen bromide at its active methylene group with a ring closure



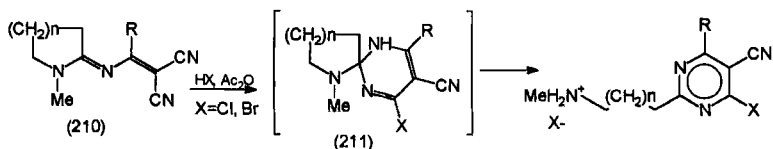
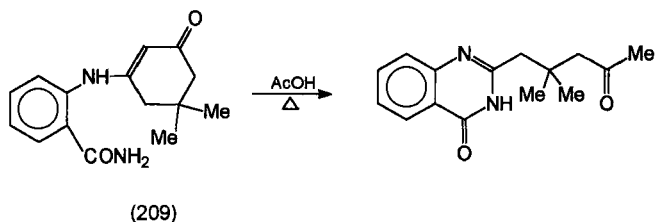
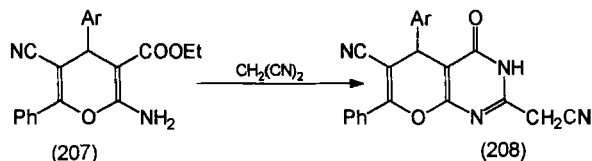
SCHEME 35

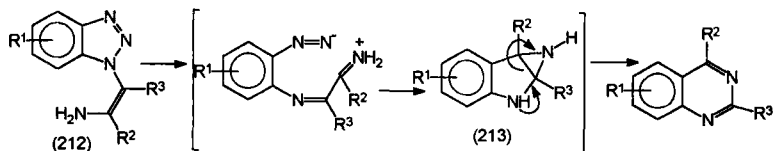


SCHEME 36

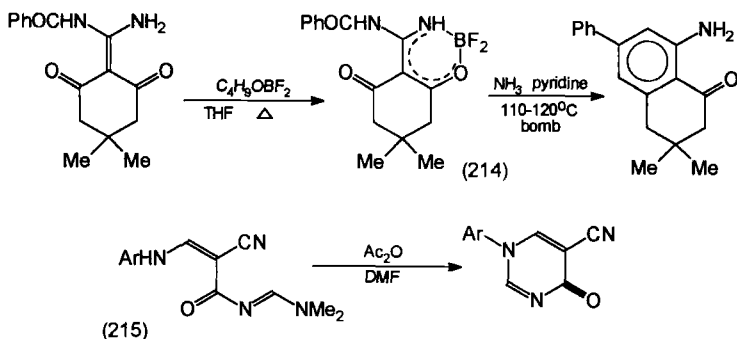


and formation of a pyrimidine (Scheme 36). An enaminoester in the pyran series (**207**) interacts with malononitrile with the formation of pyrano[2,3-*d*]pyrimidine (**208**) (92MI1). When heated in acetic acid, *N*-(*o*-carbamoyl)enaminoketones (**209**) undergo cyclization to substituted pyrimidines (94AP571). Another type of intramolecular cyclization of enamidines (**210**) on heating (93S525) proceeds through the formation of an intermediate *spiro* compound (**211**). An interesting rearrangement of benzotriazolyl-1-enamines (**212**) results in the formation of substituted quinazolines (95JOC246). The regiospecific transformation occurs with loss of nitrogen and most likely involves an aziridine intermediate (**213**).

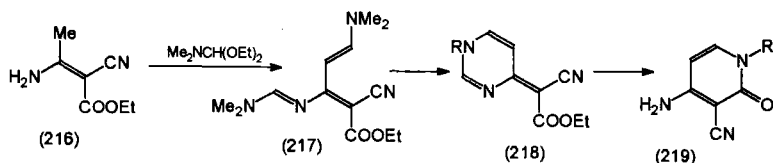




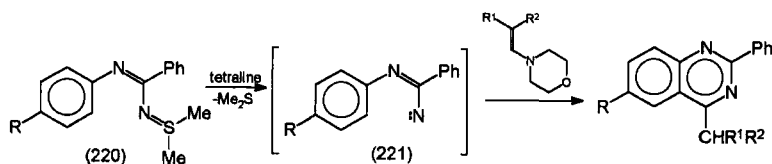
Chelate synthesis of pyrimidine derivatives, including fused pyrimidines, is based on the use of various diaminodicarbonyl compounds as starting materials (93IZV1504; 94IZV1638, 94IZV2211). The synthesis and the subsequent cyclization of the difluoroborate chelate (214) is a characteristic example (93IZV1504). Enaminoacylamidines (215) are easily transformed into 4-pyrimidinones in heated acetic anhydride (84KGS538).



A new synthesis of the pyrimidine ring from primary enaminoesters (216) proceeds through their transformation into enaminoamidines (217) and then into 4-methylenepyrimidines (218). In an alkaline medium 218 undergo a facile recyclization in high yields to the 2-pyridone derivatives 219 with an amino group in position 4 (88KGS1109). Enaminoaldehydes easily react with compounds such as guanidine or urea to afford 2-amino- and 2-oxopyrimidine derivatives (95TL205).



An unusual formation of quinazolines by reaction of benzimidodisulfimides (220) with enamines (89S214) involves an imidoynitrene (221).

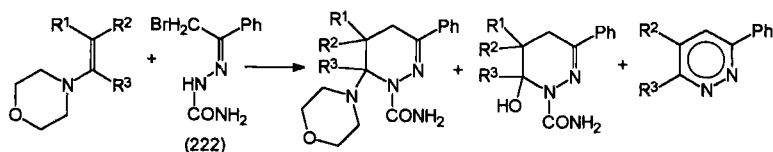


Imidazo[1,2-*a*]pyrimidines can be obtained from enediaminonitriles and *N*-acyliminoethers (96SC453). The unusual transformation of “push-pull” enamines into 4,6-dimethylamino-5-nitropyrimidine has been carried out (97KGS343). A facile synthetic method for pyrimidine derivatives based on fluorine-containing enaminketones has recently been published (97H349).

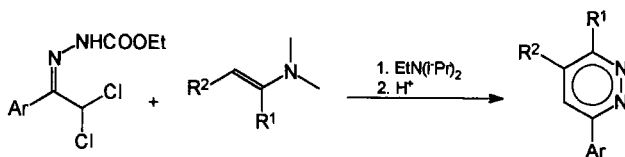
### C. OTHER AZINES

The number of studies devoted to the enamine-based synthesis of azines other than pyridines or pyrimidines is considerably smaller. Therefore, this discussion will not involve their classification into separate groups.

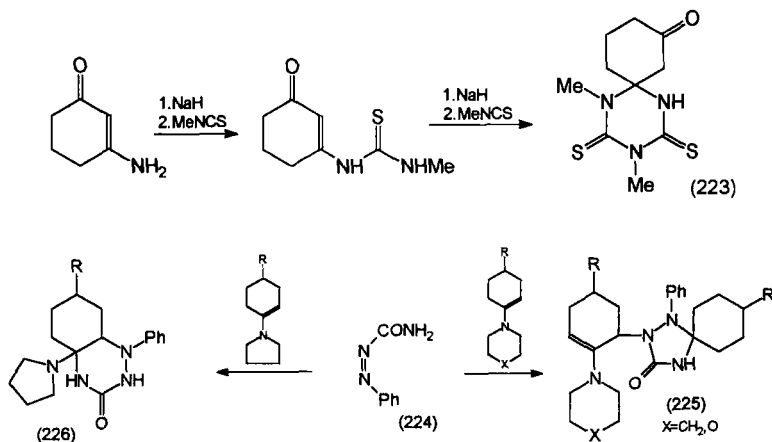
Reaction of enamines with *N*-carbamidohydrazone (222) gives a mixture of pyridazine derivatives (88G187). A new general synthesis of



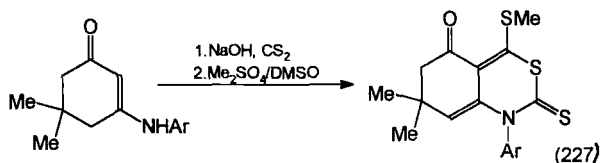
pyridazines is based on the interaction of enamines with *N*-ethoxycarbonylhydrazones of  $\alpha,\alpha$ -dichloroketones (95TL5703) (Scheme 37). Methyl isothiocyanate reacts exclusively on the nitrogen atom of primary enamines after their conversion into *N*-anions. A double reaction with methyl isothiocyanate accompanied by cyclization gives a *spiro* compound (223) with a triazine ring moiety [90JCS(P1)1869]. The formation of triazines during interaction of enamines with azidohydrazone [84JCS(P1)1427] was considered in Section III.C.



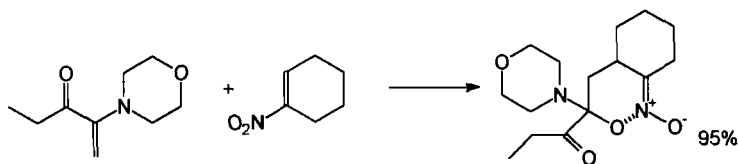
SCHEME 37



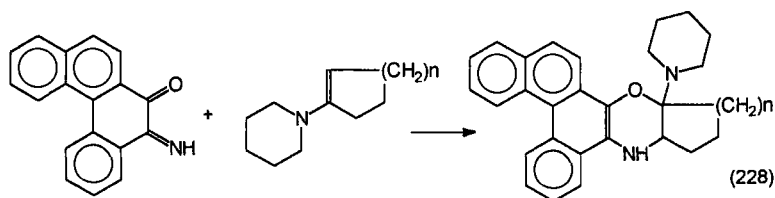
Investigation of the reactivity of phenylcarbamoyldiimide (**224**) with enamines (84G243) has established that the behavior of morpholine- and piperidine-based enamines of cyclohexanone derivatives is substantially different from those based on the pyrrolidine ring. In the first case the process leads to cyclohexane-*spiro*-triazolidinones (**225**) (83TL2909), whereas pyrrolidine-based enamines, because of their stronger nucleophilicity, react differently and give triazinones (**226**) (84G243). The reaction of enaminoketones with an excess of carbon disulfide followed by methylation with dimethyl sulfate affords 1,3-thiazine derivatives (**227**)



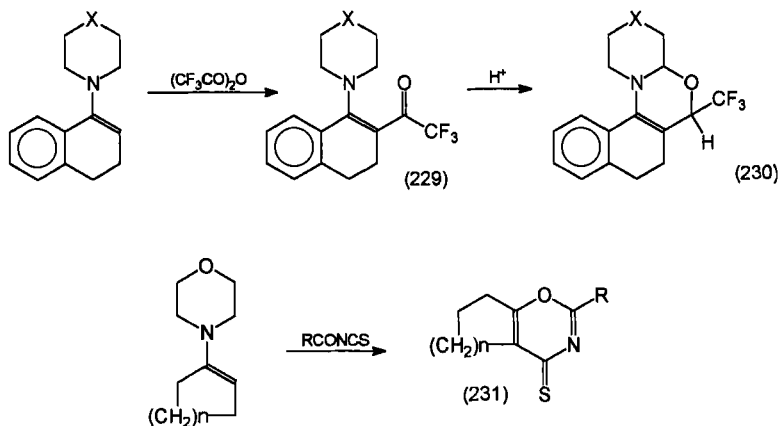
(91JHC1245). Interaction of nitroalkenes with enaminocarbonyl compounds leads to a highly diastereoselective [4 + 2]-heterocyclization with the formation of 1,2-oxazines [91JCS(P1)1645] (Scheme 38).



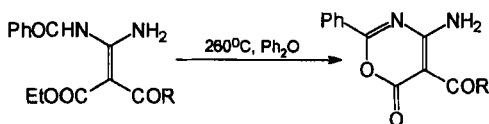
SCHEME 38



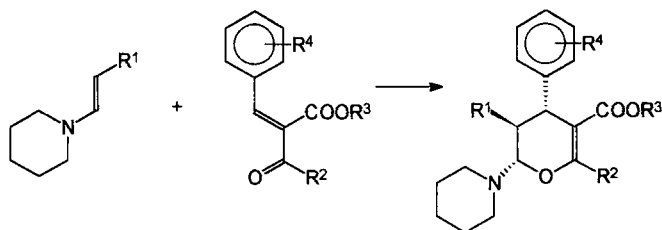
Reactions of enamines with monoimines of *o*-quinones afford polycyclic compounds **228** with an oxazine ring (86MI2). Trifluoroacetylation of enamines with trifluoroacetic acid takes place in the  $\beta$ -position of the enamine. Ketones (**229**) thus formed in an acidic medium afford fused 1,3-oxazines (**230**) (82JOC3339). Treatment of amines with silyl isothiocyanate gives not only pyrimidine derivatives but also 1,3-oxazine-4-thiones (**231**) (81CCC2696).



Heating  $\beta$ -acyl- $\beta$ -amino- $\alpha$ -benzoylaminoacrylates to high temperatures results in cyclization and formation of 2-phenyl-4-amino-5-acyl-1,3-oxazin-4-ones (94IZV1322) (Scheme 39).



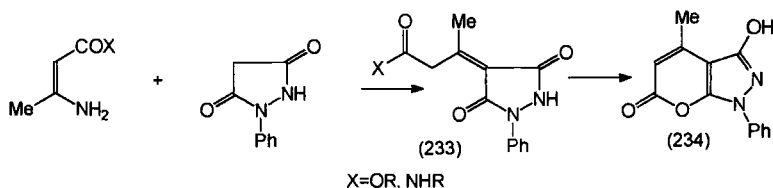
SCHEME 39



SCHEME 40

#### D. SYNTHESIS OF SUBSTITUTED PYRANS, THIOPYRANS, AND DIOXANES

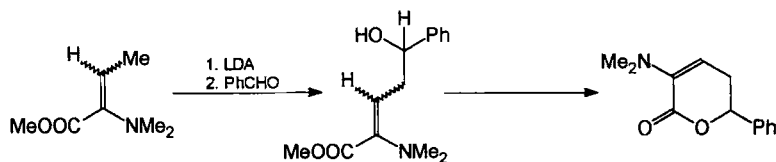
Reaction of enamines with unsaturated carbonyl or dicarbonyl compounds leads to the formation of the pyran ring [84AP861, 84BSB451; 86CB257; 89AP617; 91SC1281; 93JCS(CC)159] (Scheme 40). A second example is the reaction of enaminoketones with 1-phenyl-3,5-pyrazoline-dione giving intermediate **233**, which upon heating yields a pyrone (**234**)



(84BSB451). Metalated enamines (in the  $\alpha$ -methyl group) easily react with aldehydes, and the new enamines thus formed undergo an intramolecular cyclization giving 2-pyrone derivatives (84T733) (Scheme 41).

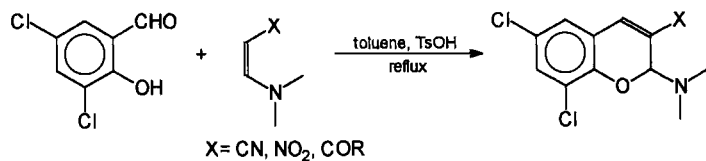
Enamine (**235**) obtained from cyclic ketones and the acetal of *N*-methyl-2-pyrrolidone gave a fused 2-pyrone [83IJC(B)1083]. 2*H*-Chromenes were obtained from 3,5-dichlorosalicylaldehyde and enamines (94RRC183) (Scheme 42). The pyran ring is formed by a reaction of animals of conjugated  $\omega$ -dimethylaminoaldehydes with cyclic  $\beta$ -dicarbonyl compounds (94IZV285) (Scheme 43).

A dienediaminodiketone derivative (**236**) obtained by heating a primary

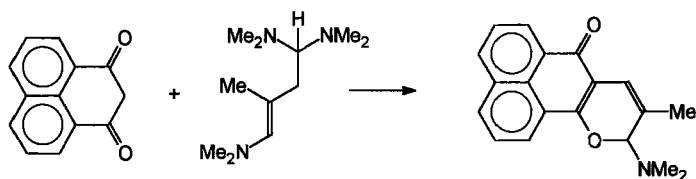


SCHEME 41

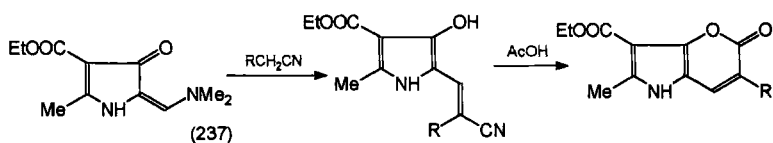
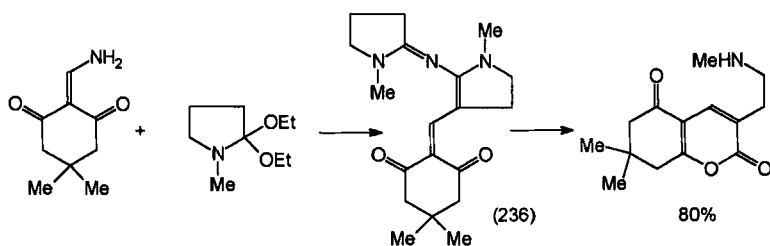
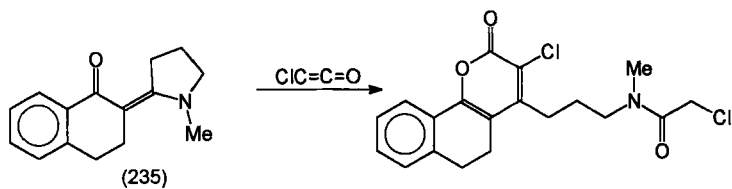




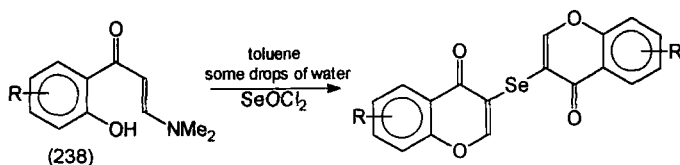
SCHEME 42



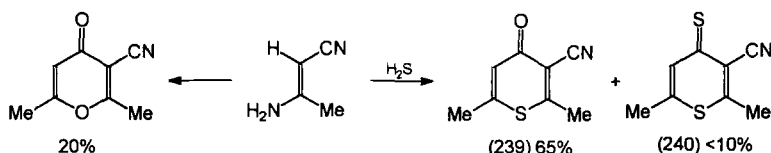
SCHEME 43



enaminoketone with the acetal of *N*-methyl-2-pyrrolidone in an acidic medium gives a coumarin derivative in a high yield (87KGS1477). Enaminoketone **237** served as the starting reactant in the synthesis of pyrrolo[3,2-*b*]pyrans [92KFZ(6)68]. Bis-chromones with a selenium bridge were obtained from enaminoketones (**238**) and selenium oxychloride (95JHC43).

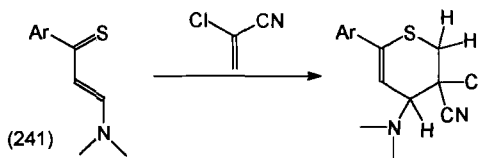


$\beta$ -Aminocrotononitrile reacts with hydrogen sulfide in an alkaline medium under phase transfer catalysis conditions and gives mainly 4-thiapyranone (**239**) with 4-thiapyranthione (**240**) as a minor product. In

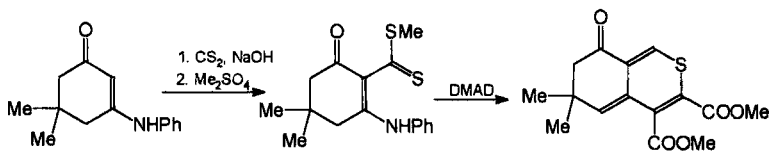


the absence of hydrogen sulfide, a low yield of 2,6-dimethyl-3-cyano-4-pyranone is obtained (85HI153). The reaction mechanism is claimed to involve the addition of the anion of hydrogen sulfide to the enamine, the formation of a thioketone, and its subsequent condensation with the starting enaminonitrile resulting in cyclization.

Reaction of enaminothiones (**241**) with electrophilic olefins, such as maleic anhydride (81TL3175) or 1-chloro-1-cyanoethylene (82T1705),



leads to a regiospecific synthesis of thiapyrans. The thione **241** also forms thiapyrans in a reaction with dimethyl acetylenedicarboxylate or with propiolic ester (82T1705). A similar course is observed in the case of the reaction of enaminothiones with esters of unsaturated acids (94JPR163). The

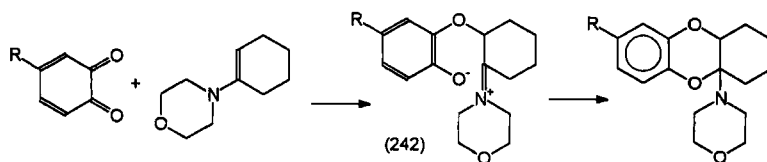


SCHEME 44

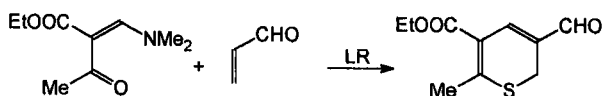
synthesis of thiapyrans has been reported (91JHC1245) (Scheme 44). The formation of thiapyrans from enaminoketones on treatment with the Lawesson reagent (LR) and then with acrolein has been described [92JCS(P1)2603] (Scheme 45).

A different route to pyrones is the preparative electrochemical oxidation of enamines in acetonitrile in the presence of tetraethylammonium perchlorate (88MI2) (Scheme 46). The synthesis of 2-pyrone derivatives has been carried out by reaction of  $\beta$ -dicarbonyl compounds with methyl- $\alpha$ -benzoylamino- $\beta$ -dimethylaminoacrylate (96JHC751). Thiapyran derivatives can be obtained by interaction of enamines based on ( $\beta$ -amino- $\alpha$ -cyanoacryloylmethyl)pyridinium chloride derivatives with carbon disulfide (95M711). The synthesis of pyridine derivatives based on analogous enamines has been described as well (95M711).

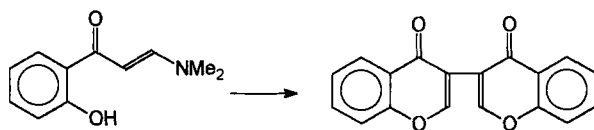
Derivatives of *o*-quinones react with enamines to form oxazines. In this reaction, *o*-quinones themselves form dioxanes [88JCS(P1)151]. The authors assume that the reaction proceeds by a stepwise [4 + 2]-cycloaddition with the formation of intermediates **242**. Dioxanes are also formed by



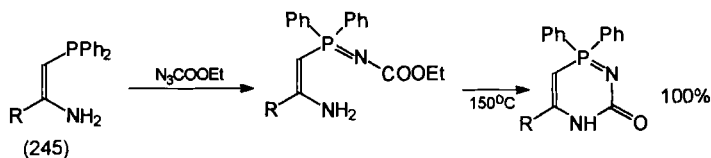
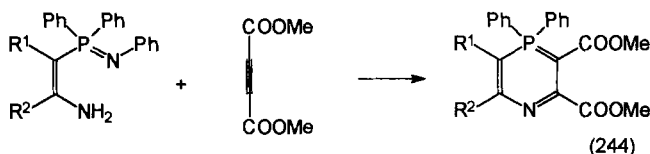
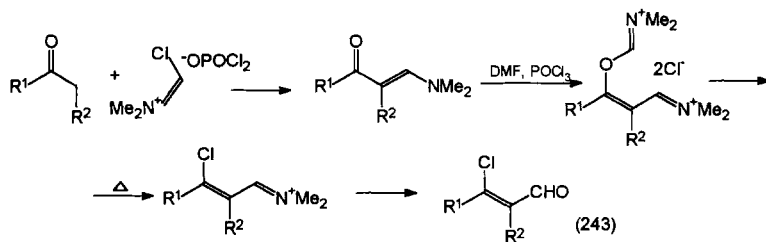
epoxidation of enamines with dimethyldioxirane. A likely reaction mechanism is shown (92CB1263) (Scheme 47). A new and efficient synthesis of  $\beta$ -chloroacroleins (**243**) as starting materials for various heterocyclic systems [88S742; 89JCS(P1)1369, 89S515, 89TL223; 91JHC999; 92T5199] has been reported (95SC1869).



SCHEME 45

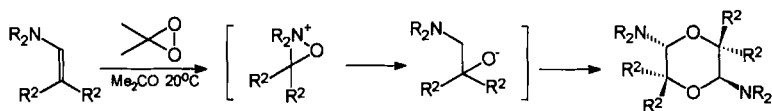


SCHEME 46

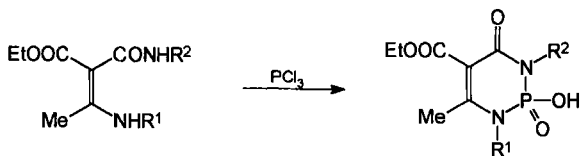


## E. SIX-MEMBERED RING PHOSPHORUS-CONTAINING HETEROCYCLES

The reaction of β-enamino-λ<sup>5</sup>-phosphanes with dimethyl acetylenedicarboxylate gives 1-aza-4λ<sup>5</sup>-phosphinines (244) [89JCS(P1)2273]. Six-membered ring phosphorus-containing heterocycles were obtained by the reaction of enaminophosphines (245) with ethyl azidoformate (87TL2875).



SCHEME 47



SCHEME 48

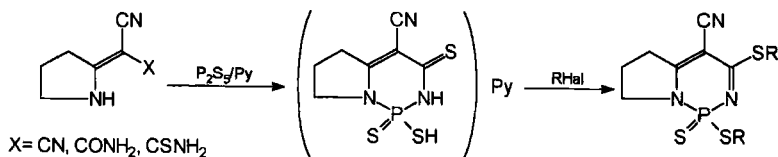
Enaminoamides with phosphorus trichloride yielded diazaphosphorins (92JPR711) (Scheme 48). Diazaphosphorins were also obtained by treatment of enamionitriles, enaminoamides, and enaminothioamides with phosphorus pentasulfide in pyridine (96MC191) (Scheme 49). Fused 3-cyano-2-pyridones react with the Lawesson reagent giving phosphorus-containing heterocycles (95MC191) (Scheme 50).

## V. Synthesis of Seven- and Eight-Membered Rings

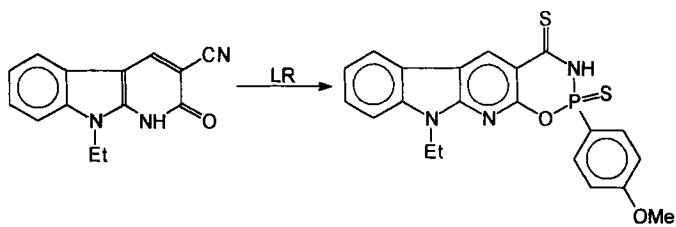
Condensation of cyclic enaminoamides (**246**) with dimethyl acetylenedicarboxylate gives 2-azepinone derivatives (**247**) (85AJC1847). Similarly, immonium salts (**248**) when treated with bases give enamines, which subsequently react with dimethyl acetylenedicarboxylate or unsaturated ketones and give azepines (81AP787). The reaction of primary enamionitriles with dimethyl acetylenedicarboxylate proceeds in a similar fashion (84CPB2596). Another route to azepines has been described (95JHC57) (Scheme 51).

Irradiation of enamines (**249**) results in processes related to reduction and cyclization reactions with the participation of the enamine  $\beta$ -carbon atom (82JOC482). A benzazepine derivative (**250**) was isolated as one of the products. Enamines (**251**) interact with aldehydes in a smooth reaction and give diazepines [84CPB3274; 91KFZ(11)16]. Benzodiazepine derivatives can be obtained in a similar fashion (95KGS336).

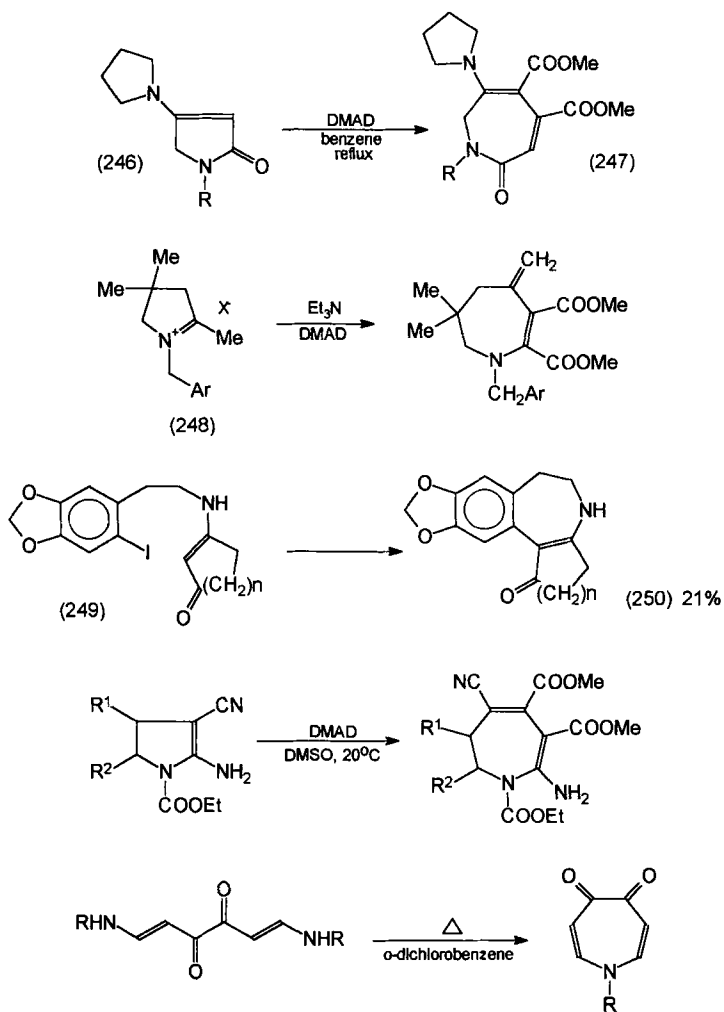
Enaminoketones (**252**) can undergo cyclization in several different ways depending on reaction conditions. Thus, in the presence of acetic



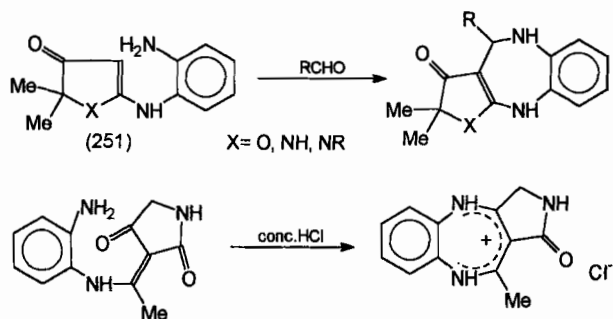
SCHEME 49



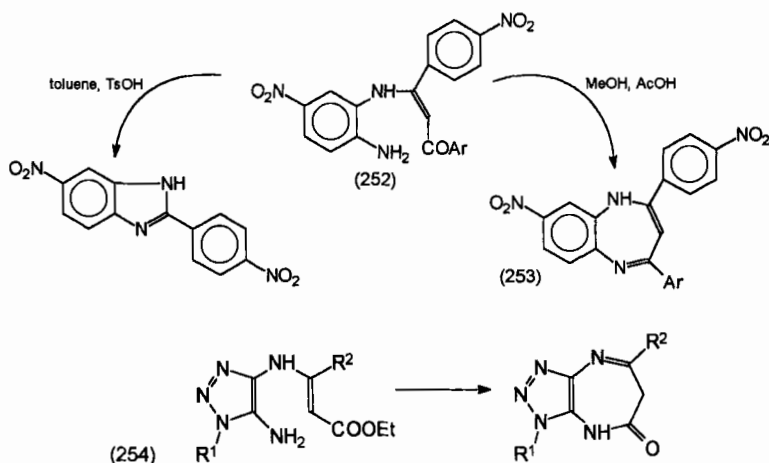
SCHEME 50



SCHEME 51



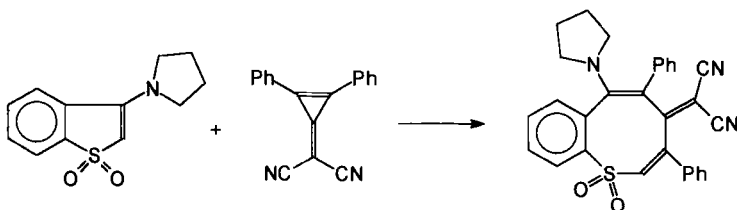
acid they give diazepine derivatives (253) whereas in the presence of *p*-toluenesulfonic acid they afford benzimidazoles (95KGS950). Triazolyl-enamines (254) undergo cyclization in the presence of sodium ethoxide and give 1,2,3-triazolo[5,4-*b*]diazepines (95JHC169). The formation of eight-



membered sulfur-containing rings is based on the interaction of enamines with dicyanomethylenecyclopropene (82CL847) (Scheme 52). The synthesis of 1,4-thiazepine-3-one (96LA211) and 1,4-thiazepine derivatives (95JHC463) from enaminothioamides has been described.

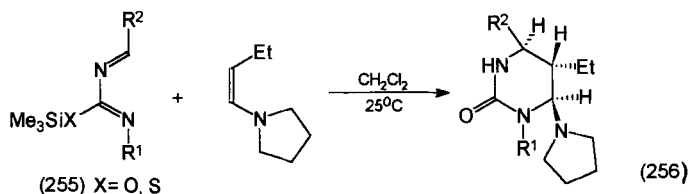
## VI. Enamines as Electron-Rich Synthons in Reactions with Electron-Deficient Azadienes

At present, researchers are attracted to the reactions of various enamines, enediamines, and related compounds with azadienes containing



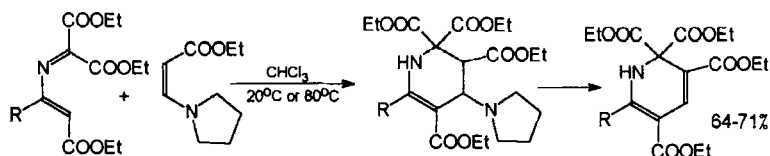
SCHEME 52

strongly electron-withdrawing groups or a formal positive charge (94MI2; 95KGS1307). Because of the numerous new heterocyclic systems obtained with this approach, an overview follows. The reactions of enamines with diene systems that do not constitute a part of any azaheterocyclic ring will be reviewed. For example, interaction of diaza-1,3-butadiene (**255**) with a pyrrolidine enamine of butyraldehyde (*E* isomer) or other enamines without an electron-withdrawing group in the  $\beta$ -position gives high yields of [4 + 2]-cycloaddition products, that is, hydrogenated pyrimidines (**256**)



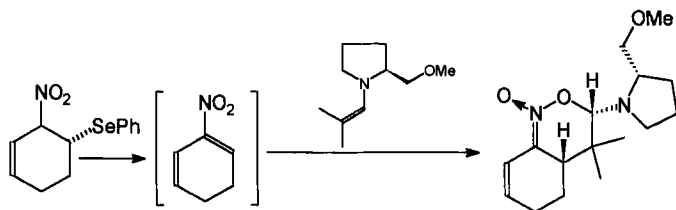
[89TL4573; 94H(37)1109]. An analogous [4 + 2]-cycloaddition is observed in the reaction of azadienes with enamines (95JOC2384). Acyclic azadienes can react with  $\beta$ -aminoesters in the same fashion (Scheme 53). Another class of compounds capable of such a reaction are dienes without aza groups but containing a strongly electron-withdrawing substituent such as the nitro group (92TL5641). In this case, the nitro group assumes the role of the terminal double bond (Scheme 54).

A special emphasis is now being placed on studies in which electron-deficient heterocycles react as dienes [82TL3965; 85H2789; 87DOK364;



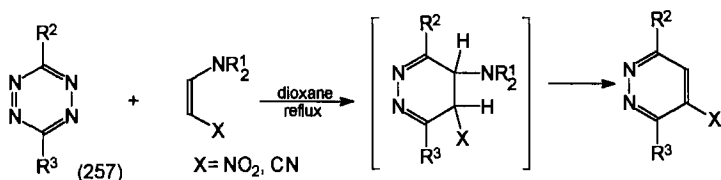
SCHEME 53



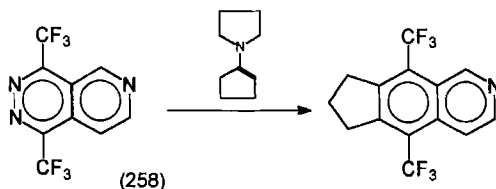


SCHEME 54

88CPB3354, 88H2213; 89NKK846, 89T2693; 91T3959; 92KGS1243, 92T7173; 94H(38)1595, 94H(38)1805, 94TL2075; 95H1445, 95H2519, 95-IZV1318, 95JOC4919, 95M211]. Diaryl- and diheteroaryltetrazines (**257**) enter into an inverse electron demand Diels–Alder reaction with  $\beta$ -cyano- and  $\beta$ -nitroenamines, resulting in a loss of nitrogen and the for-

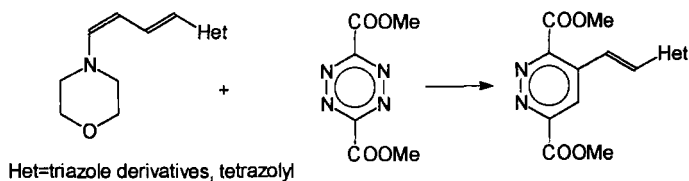


mation of pyridazine derivatives (85H683). Cyclic enamines react with bis-trifluoromethyltetrazine similarly and yield fused pyridazines [94-H(38)1845]. An appropriate choice of starting enamines made possible the synthesis of a series of fused pyridazines. A related reaction using (**258**) has been described [94H(38)1845]. An analogous reaction between



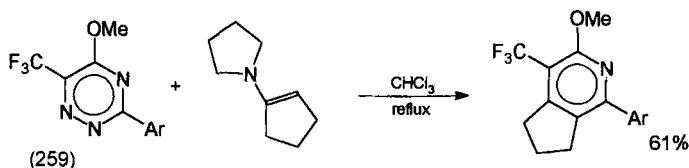
dienamines and 3,6-dimethoxycarbonyltetrazine is observed (95JOC4919) (Scheme 55).

1,2,3-Triazines on reaction with enamines followed by loss of a nitrogen from the intermediates give pyridine derivatives (85H2789) (Scheme 56). The reaction of 1,3,5-triazine with enamine and enaminoester hydrochlorides in acetonitrile leads to mixtures containing pyrimidines and pyridines



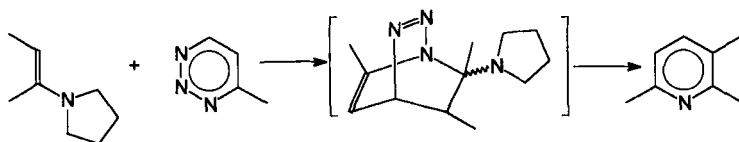
SCHEME 55

(87DOK364) (Scheme 57). Using  $^{15}\text{N}$ -labeled enamines, it was possible to demonstrate that the resulting pyrimidines contain 63% of the  $^{15}\text{N}$  label. Therefore, the authors assume (92KGS1243) that this process involves initial protonation of the triazine and activation of the ring toward nucleophilic attack on the  $\beta$ -position of the enamine (label is preserved, pathway **A**) and cycloaddition in an inverse Diels–Alder reaction (label is lost, pathway **B**) (Scheme 58). Reactions of 1,2,4-triazines (**259**) with enamines also were studied (88CPB3354). The alkaloids onychine and 6-methoxyonychine were synthesized using this methodology (88H2213).

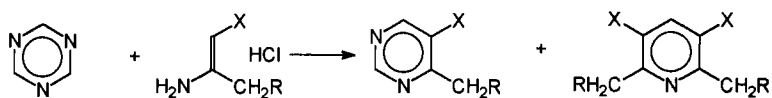


Pyrimidines are expected to be much less reactive in cycloadditions of this type than triazines and tetrazines. Normally, the presence of electron-withdrawing substituents on the pyrimidine ring is essential. The best results are obtained with a nitro group in position 5. Reaction of 5-nitropyrimidine with various enamines affords fused nitropyridines (82TL3965; 89T2693) (Scheme 59). The mechanism (89T2693) is in agreement with the usual expectations.

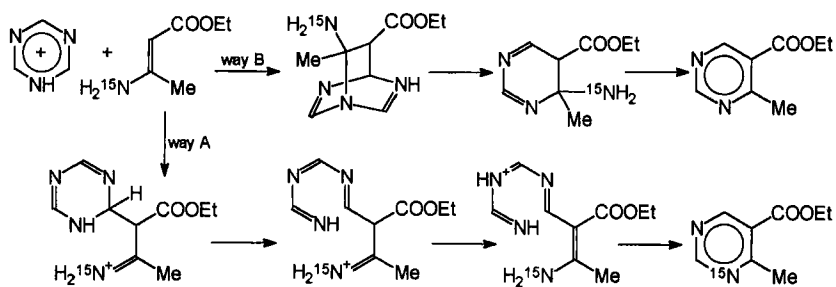
5-Nitropyrimidine reacts in analogous fashion with enamines based on macrocyclic ketones (94TL2075). Quaternization makes it possible for 1-methylpyridinium iodide to react with enaminoesters with the formation of



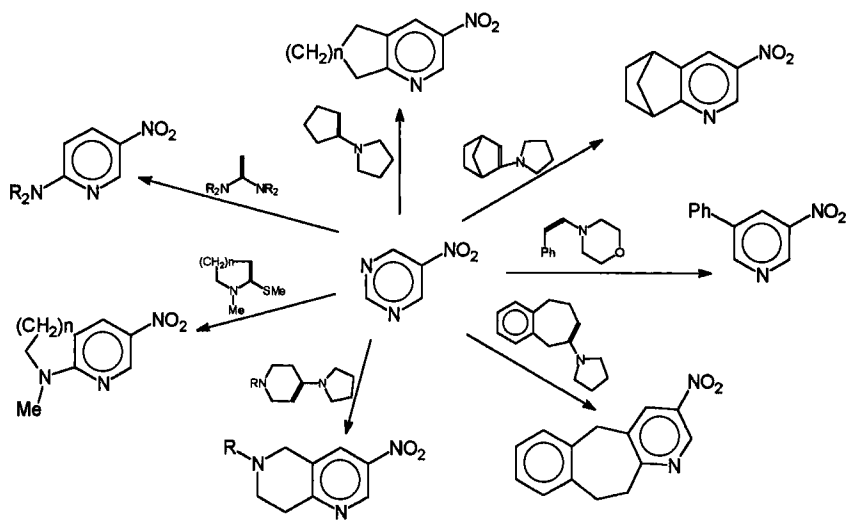
SCHEME 56



SCHEME 57



SCHEME 58

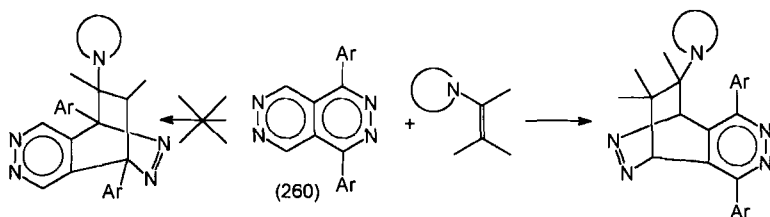


SCHEME 59

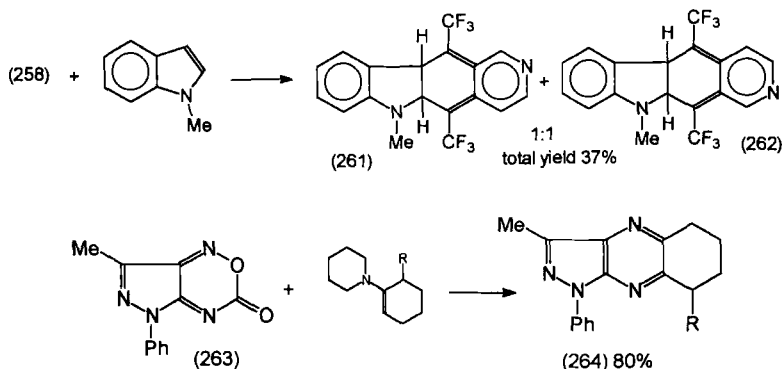
pyridine derivatives (95IZV1318). Anthranils (89NKK846) and furoxans (86CB257) can also react with enamines, giving fused quinoline *N*-oxides and quinoxaline *N,N'*-dioxides.

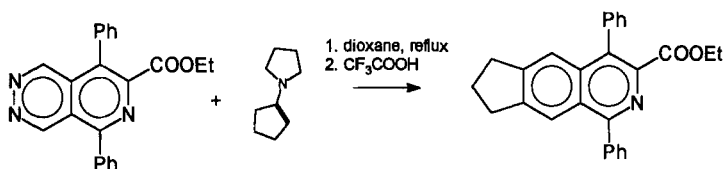
For steric reasons, the reaction of enamines with 1,4-diarylpyridazino-[4,5-*d*]pyridazines (**260**) takes place only with the unsubstituted pyridazine ring (91T3959). Numerous enamines were used in the reaction with **260**. Among other products, a series of phthalazine derivatives was obtained.

An efficient approach to isoquinoline derivatives is based on the reaction



of enamines with substituted pyrido[3,4-*b*]pyridazines (92T7173) (Scheme 60). Reactions of other substrates with enamines confirm these results and have been used to synthesize various fused indoloisoquinolines including partially hydrogenated rings (95H1445). When 1-methylindole was used as the enamine, an isomeric (1 : 1) mixture of dihydroindoloisoquinolines **261** and **262** was obtained along with other products (95H1445). A very similar situation is observed in the reaction of pyrido[2,3-*d*]pyridazines with enamines leading to quinoline derivatives (95M211). When pyridazino[4,5-*b*]indoles are heated with enamines, they undergo a thermally induced inverse electron demand Diels–Alder reaction leading to carbazole derivatives [94H(38)1805]. The reaction of an oxadiazinone derivative **263** with enamines gives fused pyrazines (**264**) (93JOC6155).





SCHEME 60

## VII. Conclusion

There is a rich synthetic potential for enamines in heterocyclic synthesis. Enamines can react as electrophiles or nucleophiles and as new partners in cycloaddition reactions. Various derivatives of nitrogen-, oxygen-, and sulfur-containing heterocycles have been prepared, and these, in turn, are of interest as starting materials for additional syntheses. They represent potential synthons for the development of various new directions in organic chemistry.

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# Fragmentations of Five-Membered Rings

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I. Introduction .....	361
A. Thermolysis and Pyrolysis .....	362
B. Shock Waves .....	363
C. Photolysis .....	363
D. Electron Impact Ionization .....	364
E. Other Techniques .....	364
II. Fragmentation of Five-Membered Rings: Overview .....	364
III. [5 → 5] Isomerizations .....	367
IV. [5 → 4 + 1] Fragmentations .....	369
V. [5 → 3 + 2] Fragmentations .....	370
A. Ring Contraction (Least-Motion Path) .....	371
B. Ring Contraction (Non-Least-Motion Path) .....	375
C. Selectivity in Ring Contraction Reactions .....	381
D. [5 → 3 + 2] Cycloreversion .....	383
E. Other [5 → 3 + 2] Fragmentations .....	390
VI. [5 → 2 + 2 + 1] Fragmentations .....	398
VII. [5 → 2 + 1 + 1 + 1] and [5 → 1 + 1 + 1 + 1 + 1] Fragmentations .....	404
VIII. Conclusions .....	404
References .....	406

## I. Introduction

*Thermolysis* is defined as the uncatalyzed spontaneous fragmentation of organic compounds initiated by thermal energy. At higher temperatures (i.e., under even more stringent conditions) this process usually is termed *pyrolysis*. Both methods may be used either for the generation of otherwise inaccessible compounds (e.g., highly reactive species) or for the study of thermal properties and thermal decomposition reactions of molecules. The latter aspect has recently been of special interest in the investigation of reactions with femtosecond kinetics. Provided that an associative reaction and its reversal, the retrograde dissociative reaction, follow the same mechanism, either of them may be used for mechanistic studies. So, the retro-

Diels–Alder reaction, for example, is much better suited as a unimolecular reaction than the bimolecular cycloaddition because the former allows better control of precursors, in which the structural properties are well defined (96JA8755). Fragmentation of a molecule may be initiated by various methods depending on how the required energy is supplied.

### A. THERMOLYSIS AND PYROLYSIS

Thermal fragmentation of a molecule is conveniently accomplished under high vacuum and short contact times by the technique usually termed flash vacuum pyrolysis (FVP) [77AG377, 77AG(E)365; 80MI1; 82RTC317,365; 84MI1; 86AG413, 86AG(E)414]. Most frequently, precursor molecules are degraded to smaller molecules with unusual structural features that prevent their generation by common synthetic routes. In combination with low-temperature matrix techniques, semistable or even unstable species may be obtained that are short-lived under ordinary conditions (95MI1). That even large stable molecules may be formed at high temperatures has recently been demonstrated spectacularly by the generation of fullerenes, which opened an entirely new branch of chemistry (94MI1).

Obviously, gas-phase pyrolysis and thermolysis are restricted to volatile compounds. On the other hand, thermal decomposition reactions can also be investigated in solution and even in the solid state (80MI1). Often, reactions initiated under these conditions are the reversal of well-known reactions. Thus, for all associative thermal reactions that occur at moderate temperatures, at least in principle, the corresponding retroreaction is favored at elevated temperatures. This holds particularly for thermal pericyclic reactions, although it may be difficult, if not impossible, to observe this retrograde reaction directly because other, competitive reactions may occur [86AG413, 86AG(E)414; 90MI2; 90MI3].

The combination of FVP with photoelectron spectroscopy (PES) makes it possible to investigate gas-phase pyrolysis reactions without isolation of the products [81AG425, 81AG(E)427; 88MI1]. Gas analysis of complex mixtures in real-time is not an easy task. By PES the components are identified by their characteristic ionization peaks. This is quite easy for small, unsaturated molecules containing heteroatoms such as nitrogen, oxygen, or sulfur. Multicomponent systems with up to about ten different products can be identified simultaneously (97JHC113). Such a system probably would have caused severe difficulties for most analytical real-time methods. This method has also been used to study transient species (79MI1; 91MI1). Thermolysis takes place at temperatures between 20 and 1100°C in the PE spectrometer just before photoionization, and the spectrum of the product

mixture is recorded at a constant particle flow. Thus, it is quite easy to investigate and optimize pyrolysis reactions, even when there are several reaction steps and various reaction paths.

## B. SHOCK WAVES

Shock-wave techniques (81MI1; 90ARP559) can be used to study the kinetics of fast reactions in the gas phase at high temperatures, and this method was successfully applied to the pyrolysis of several heterocyclic compounds including five-membered rings. The temperature of the gas can be changed very quickly to an arbitrarily high value. Typical conditions are gas densities of about  $10^{-5} \text{ mol} \cdot \text{cm}^{-3}$  and temperatures of 800–1600 K. Most frequently, several reaction channels for decomposition are populated simultaneously by shock heating. The experiment is performed in a shock tube, which is a tube separated into two compartments by a diaphragm. If one of the compartments is pressurized and the other is maintained at lower pressure, the breaking of the diaphragm leads to a shock wave through the low-pressure gas. With the shock wave a temperature step will pass through the gas. The shock tube can thus be considered to be a “millisecond high-temperature furnace.” Spectroscopic methods are used to follow the chemical changes during the experiment, and all the tools of modern analytical chemistry can be employed for product analysis after the experiment.

## C. PHOTOLYSIS

When a molecule is excited to an antibonding electronic state by absorption of electromagnetic radiation, this process usually leads to decomposition (90MI1; 95MI2). Well-known examples are the photolytic fragmentation of diazo compounds, diazirines, and ketones (Norrish-type reactions). A mercury discharge lamp emitting much of its light at 253.7 nm, which corresponds to an energy of  $473 \text{ kJ} \cdot \text{mol}^{-1}$ , is capable of causing homolysis of most of the bonds usually occurring in organic molecules. Product formation is influenced by the reaction conditions, in particular by the wavelength and intensity of the radiation. Selective photolytic reactions may be initiated by exciting the molecules to definite electronic states (singlet or triplet) with light of the appropriate wavelength, if necessary in the presence of a sensitizer. In general, photolysis leads to products other than those in thermolysis.

#### D. ELECTRON IMPACT IONIZATION

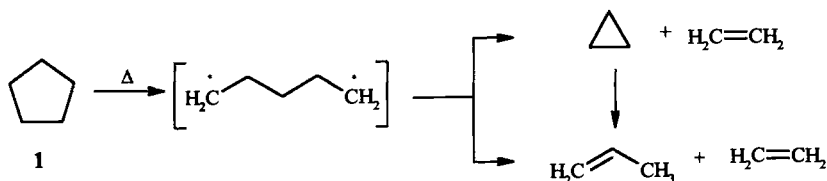
By this technique, which is common in mass spectrometry, molecules are hit by electrons of high kinetic energy (usually 70 eV) and are transformed to radical cations in thermally high excited states of limited stability, because simple ionization requires only an energy of about 10 eV (78MI1). Many decompositions initiated by this technique (e.g., retrocycloadditions) resemble ordinary thermal reactions (86MI1). Special techniques such as collisional activation mass spectrometry [76AG589, 76AG(E)509] and tandem mass spectrometry (83MI1; 88MI2) are available to study the fragmentation of molecular ions. Because of possible correlations between mass spectral and pyrolytic fragmentation, the mass spectrometric study is often the starting point for acquiring some information about the decomposition mechanism.

#### E. OTHER TECHNIQUES

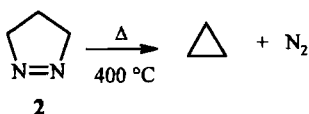
Microwave discharge can be used to create a plasma with a very high temperature that can cause dramatic fragmentation and recombination reactions of molecules in the gas phase (93MI1). By irradiation of a liquid or solution with ultrasound, cavities are generated in which for a very short time ( $10^{-6}$  s) temperatures of about 5000 K and pressures of many hundred bars are produced. These conditions are more than sufficient to degrade organic molecules, and methods have been developed to perform this decomposition in a controlled manner [sonochemistry (89S787; 97MI1)]. However, it appears that these techniques have not been used for systematic studies concerning fragmentation of five-membered ring compounds.

### II. Fragmentation of Five-Membered Rings: Overview

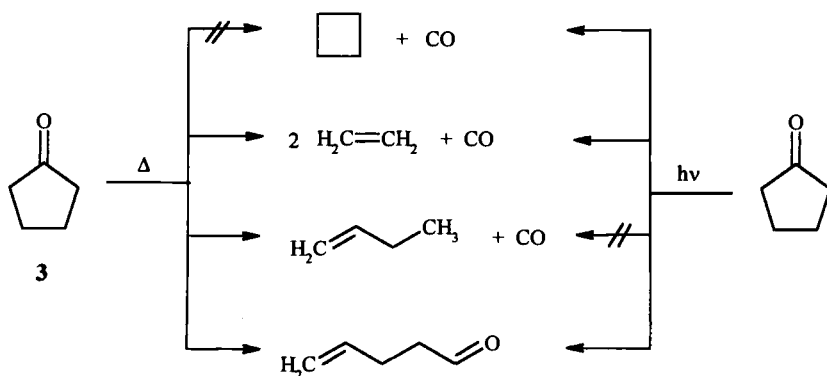
In principle, several different reactions are possible for the fragmentation of five-membered rings; the type depends largely on the structure of the molecule, in particular on the degree of unsaturation and the kind, number, and position of heteroatoms and substituents. For a saturated ring, homo- or heterolytic cleavage of a single bond, which will afford a 1,5-diradical or a 1,5-zwitterion, is most likely. Subsequently, these primary products will convert to more stable products. As an example, this process is illustrated for cyclopentane (**1**), which affords ethene and cyclopropane or propene (86JPC419). This reaction is also observed in the fragmentation induced by electron impact ionization of **1**.



Such a ring contraction will be much easier when a stable leaving group is already present in the starting compound (e.g.,  $\Delta^1$ -pyrazoline, **2**). Cyclic azocompounds are well suited for such reactions [77AG876, 77AG(E)835; 80CRV99; 93JCS(P2)405].

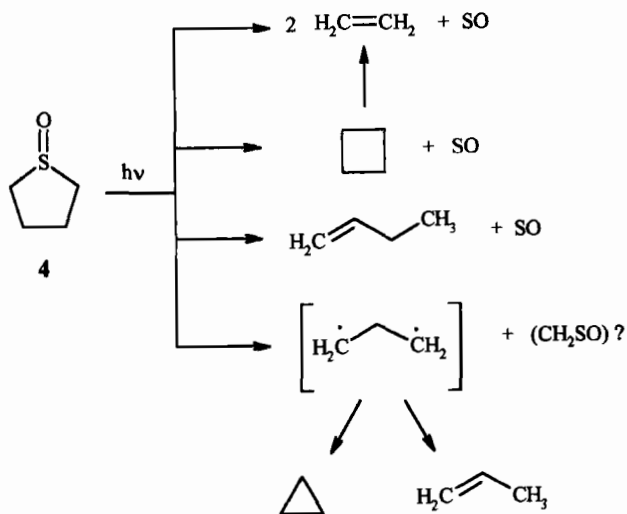


In an analogous reaction, cyclobutane can be formed from cyclopentanone (**3**) by extrusion of carbon monoxide. However, this is not the case in the thermal decomposition of **3**: Ethene is obtained in addition to other acyclic products such as 1-butene and 1-penten-5-al (69JA7645). On the other hand, ring contraction to cyclobutane occurs, among other reactions, in the photolysis of **3** (70CJC2269, 70JPC1432. In both pyrolytic and photolytic decomposition, there are three main paths of fragmentation, with the difference that cyclobutane is generated only photochemically and 1-butene only thermally. The five-membered ring is split into fragments containing one, two, or four ring atoms.



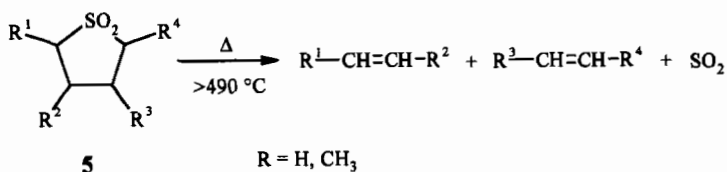
A similar number of different reaction channels are populated in the photolysis of the related thiolane 1-oxide (tetrahydrothiophene 1-oxide, **4**) (80JPC1302). However, in this case also cyclopropane and propene are



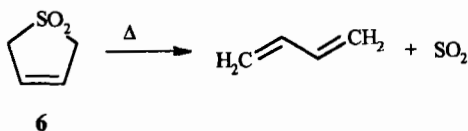


generated by breaking the five-membered ring into a three- and a two-membered fragment.

Simple sulfolanes (thiolane 1-dioxides, tetrahydrothiophene 1,1-dioxides, **5**) show a more uniform mode of fragmentation into a one- and 2 two-membered fragments; they are cleaved into sulfur dioxide and two alkenes [75JOC1842; 94JCS(P1)2301].<sup>1</sup>



Sulfolene (2,5-dihydrothiophene 1,1-dioxide, **6**) is well known to afford 1,3-butadiene and sulfur dioxide in a retrocheletropic cycloaddition (77MI1).



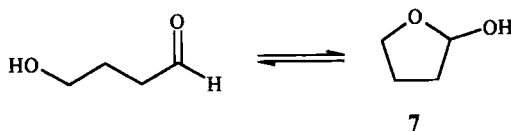
<sup>1</sup> The extrusion of  $\text{SO}_2$  from heterocyclic five-membered rings was recently reviewed by Aitken *et al.* (93PHC).

Direct cleavage of a five-membered ring into fragments of two- and three-ring atoms occurs in the reversal of 1,3-dipolar cycloadditions [79AG781, 79AG(E)721; 84MI3]. This reaction is likely to occur when both fragments are stable (i.e., low-energy) molecules or will readily convert to such species.

In the following sections fragmentation reactions are classified according to the size of the fragments generated from the five-membered ring irrespective of the mechanism by which this process occurs. So, in principle we may find  $[5 \rightarrow 4 + 1]$ ,  $[5 \rightarrow 3 + 2]$ ,  $[5 \rightarrow 3 + 1 + 1]$ ,  $[5 \rightarrow 2 + 2 + 1]$ ,  $[5 \rightarrow 2 + 1 + 1 + 1]$  and  $[5 \rightarrow 1 + 1 + 1 + 1 + 1]$  splittings. A simple ring-opening reaction (followed by rearrangement) such as the formation of 1-penten-5-al from cyclopentanone (**3**) is classified as  $[5 \rightarrow 5]$ . In cases in which several different fragmentations occur simultaneously, the reaction is usually recorded under the most important process. This article is restricted to monocycles, and emphasis is given to thermolytic reactions.

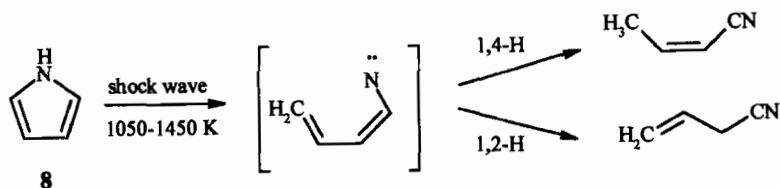
### III. $[5 \rightarrow 5]$ Isomerizations

Ring-opening reactions without further fragmentation are not very common in monocyclic five-membered ring compounds. The reaction usually must be accompanied by rearrangement of the primary intermediate to afford a stable product. Usually this implies a hydrogen or alkyl shift or transfer. Both steps, ring cleavage and rearrangement, may occur in a concerted manner. The aforementioned formation of 1-penten-5-al from cyclopentanone (**3**) involves  $\alpha$ -cleavage and hydrogen transfer. Of course, ring-opening reactions may be considered to be the reversal of cyclization reactions, which can occur either as electrocyclic reactions or as intramolecular additions.<sup>2</sup> A typical example of a ring-chain isomeric interconversion involving a five-membered ring is the equilibration of 4-hydroxybutanal and its cyclic hemiacetal 2-hydroxytetrahydrofuran (**7**); the equilibrium constant in aqueous dioxan solution is 7.8 (52JA5324). Such reactions usually follow a multistep mechanism, however, and the ring opening cannot simply be induced thermally.

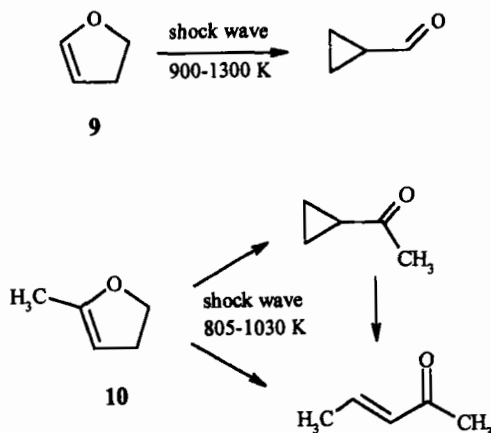


<sup>2</sup> The latter type of reaction was reviewed by Valters and Flitsch (85MI1).

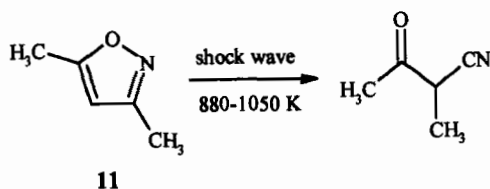
In the pyrolysis of pyrrole (**8**), two isomerization reactions are observed by which *cis*-crotononitrile and allyl cyanide are produced (89JPC5802).



The major reaction in the thermal decomposition of 2,3-dihydrofuran (**9**) is a unimolecular isomerization to cyclopropanecarboxaldehyde (89JPC-1139). In an analogous [1,3] sigmatropic reaction, the isomerization of 2-methyl-4,5-dihydrofuran (**10**) leads to acetylcyclopropane, which can rearrange to 3-penten-2-one (94JPC2341). The latter product may also be formed directly from **10**.



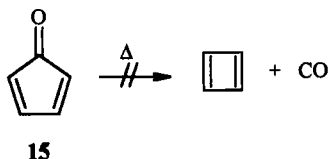
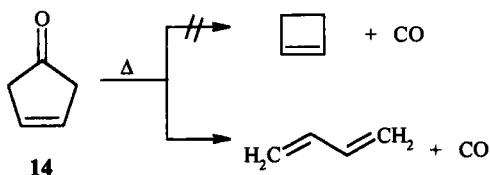
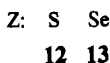
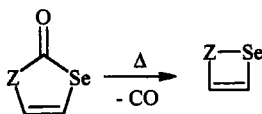
The main thermal reaction of 3,5-dimethylisoxazole (**11**) is an isomerization to 2-methyl-3-oxobutyronitrile (95JPC11436). This process involves cleavage of the N-O bond and migration of one methyl group.



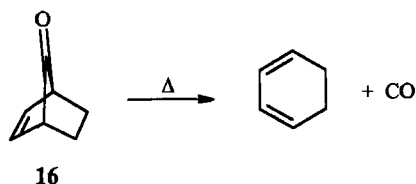
#### IV. [5 → 4 + 1] Fragmentations

The retrocheletropic fragmentation of sulfolene (**6**) into 1,3-butadiene and sulfur dioxide, and the fragmentation of cyclopentanone (**3**) into 1-butene and carbon monoxide, which have already been mentioned (see Section II), are examples of two different decomposition mechanisms of this type of splitting. Whereas the former reaction is a pericyclic ring scission, which is allowed as a thermal reaction according to the Woodward–Hoffmann rules, the latter can only proceed by at least two steps involving a 1,4-diradical as a reactive intermediate that prefers reactions other than recyclization (69JA7645). Photolytic ring contraction yielding cyclobutane as one of several reaction modes is possible in cyclopentanone (**3**) (70CJC2269, 70JPC1432) and thiolane 1-oxide (**4**) (80JPC1302).

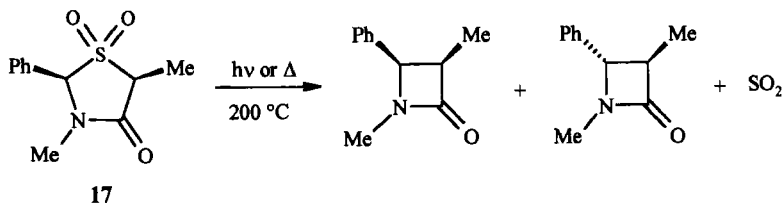
Ring contraction of a five- to a four-membered ring is not common in monocyclic systems. Two examples that have been uncovered by Schweig and co-workers using FVP/PES are the reactions of 1,3-thiaselenol-2-one (**12**) and of 1,3-diselen-2-one (**13**) to give 1,2-thiaselenete and 1,2-diselenete, respectively [87AG348, 87AG(E)343]. Cyclopenten-4-one (**14**) does not contract to cyclobutene but is split into 1,2-butadiene (86CP307; 90JA5089). The extremely unstable compound cyclopentadienone (**15**), which has been generated and observed under matrix isolation conditions (85CB3196), cannot thermally be decarbonylated to cyclobutadiene [78ZN(A)383].



On the other hand, in bi- or polycyclic molecules a decarbonylation reaction such as a  $[5 \rightarrow 4 + 1]$  fragmentation of a five-membered ring is quite common. However, in these cases the reaction is not accompanied by ring contraction. As an example, norbornen-7-one (**16**) affords cyclohexadiene (86CP307; 90JA5089).



Extrusion of sulfur dioxide from 1,3-thiazolidin-4-ones 1,1-dioxides (**17**) can be used in the synthesis of  $\beta$ -lactams (83JOC494).



## V. $[5 \rightarrow 3 + 2]$ Fragmentations

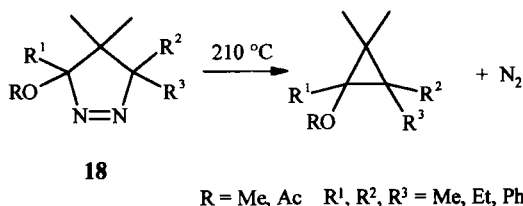
This type of ring fragmentation is by far the prevailing path of decomposition of five-membered rings. It may occur as a concerted 1,3-dipolar cycloreversion (79AG781, 79AG(E)721; 84MI3) or as a stepwise ring contraction affording a three-membered ring. Depending on the substitution of the three-membered fragment, cyclization may also lead to a new compound in which a formerly exocyclic atom becomes a member of the new ring. Prototypes of these reactions are the decomposition of pyrazoline (**2**) (93CB2675), 2,5-dihydro-1,3,4-thiadiazoles (**23**) (93CB2675), pyrazolin-4-ones (**27**) (88CB1213), and -thiones (**35**) (90CB1161), all of which show ring contraction. Although in the reaction of ketone **27** recyclization occurs directly on the least-motion path, the analogous thione **35** affords a 2-alkylidenethiirane on a non-least-motion path by which the originally exocyclic sulfur atom becomes a member of the new ring while a former ring carbon atom moves to an exocyclic position. Instead of recyclization, the reactive intermediate generated in the stepwise fragmentation may undergo rearrangement to an acyclic product. The formation of propene and

formaldehyde from tetrahydrofuran (THF, **52**) is an example of such a reaction.

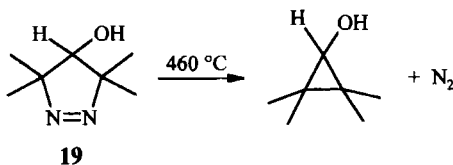
### A. RING CONTRACTION (LEAST-MOTION PATH)

As mentioned in Section III, pyrazoline (**2**) and its derivatives such as **19** are well suited for this type of reaction (93CB2675). The *cis*-azo group may be regarded as a masked nitrogen molecule that can be split off at higher temperatures or on irradiation (88JA4748). This leads to reactive species, often described as 1,3-diradicals, which afford a wide range of products, depending on substitution and reaction conditions (89CRV521). After elimination of molecular nitrogen from  $\Delta^1$ -pyrazoline (**2**), only trimethylene remains. This forms cyclopropane, unequivocally identified, and there is no other product, although a trace of propene, which has been observed by Crawford and Mishra (66JA3963) in a pyrolysis at 223°C, cannot be excluded (93CB2675).

From the correspondingly substituted  $\Delta^1$ -pyrazolines (**18**), 1-alkoxy- and 1-acetoxy-1,2,2,3,3-pentasubstituted cyclopropanes were obtained in good yields by thermolysis in cyclohexane solution under nitrogen using a high-pressure vessel (91JHC1773).



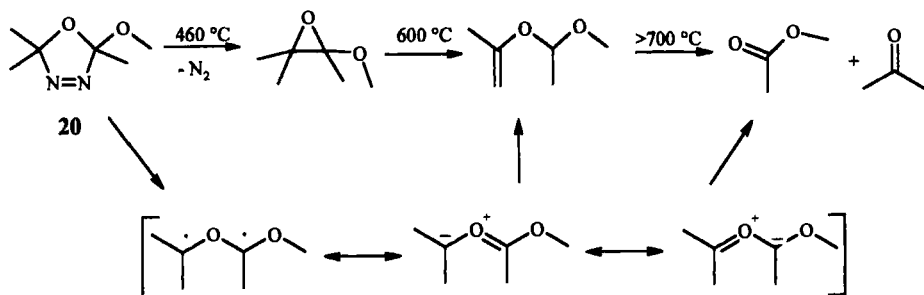
3,5-Dihydro-4-hydroxy-3,3,5,5-tetramethyl-4*H*-pyrazole (**19**) follows the same pattern as the parent compound **2** (93CB2675). The cyclopropanol is stable under the reaction conditions.



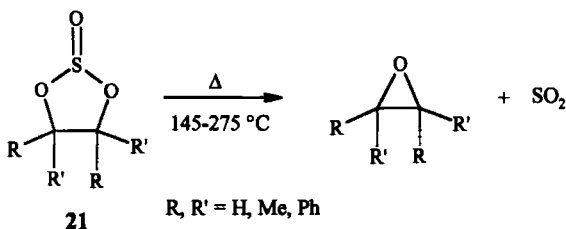
There may also be further heteroatoms in the ring, so 1,3,4-oxadiazolines (**20**) (93CB2675), 1,3,4-thiadiazolines (**22**, **23**) (93CB2675; 94CB2527), and certain tetrazolines (**24**) (88CB1213) show such a reaction. Tetrazolines

without an aryl group on N-1 or N-4 undergo, however, [3 + 2] cycloreversion (discussed later).

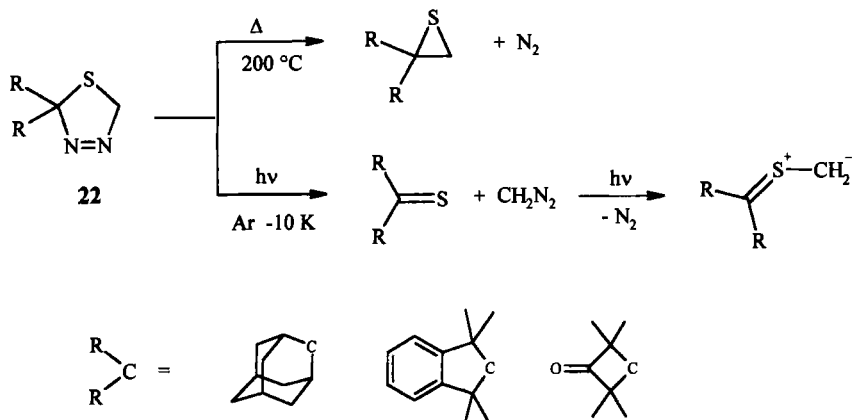
Warkentin *et al.* (82CJC2914) have studied the thermolysis of 2,5-dihydro-2-methoxy-2,5,5-trimethyl-1*H*-1,3,4-oxadiazole (**20**) at 380°C in a quartz tube, at 80°C in a sealed flask, and in CCl<sub>4</sub> solution. The results vary considerably because of the different conditions. They have determined the products from the gas-phase pyrolysis by <sup>1</sup>H NMR spectroscopy. In addition, the authors have monitored the thermolysis by PE spectroscopy. By GC they found three products, namely 1-methoxy-1-(1-propenyloxy)ethane (70%), methyl acetate (20%), and acetone (10%), in the 380°C pyrolysis product mixture. This result was confirmed by a FVP study of oxadiazolidine **20** at 350 and 510°C that gave the same products (93CB2675). The latter two compounds are secondary products that are formed from the primary reaction product methoxytrimethyloxirane. However, there is evidence for the formation of a carbonyl ylide as a transient species in solution (82CJC2914; 92JA8751). Adam and Finzel (90TL863) have observed diazo compounds and methyl acetate in the benzophenone-sensitized photolysis of Δ<sup>3</sup>-1,3,4-oxadiazolines, but not in thermolysis.



1,3,2-Dioxathiolane 2-oxides (1,2-diol cyclic sulfites, **21**) can be converted to oxiranes (72JOC2589).

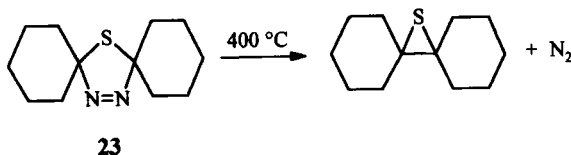


Thermolysis of thiadiazolines (**22**) in solution or under FVP conditions yields the corresponding thiiranes exclusively, whereas matrix photolysis in an organic glass or in solid argon allows the detection of thiocarbonyl ylides



(94CB2527). The latter are formed in a stepwise manner and are not directly formed from the educts by a simple extrusion of  $\text{N}_2$ . In the first step a fragmentation into thioketones and diazomethane occurs, followed by the generation of methylene from diazomethane. Addition of methylene to the thioketones finally leads to the ylides.<sup>3</sup>

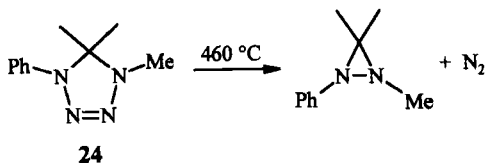
The thermolysis of 7-thia-14,15-diaza-dispiro[5.1.5.2]pentadec-14-ene (**23**) at  $110^\circ\text{C}$  in solution has been studied by Barton and Willis (72JCS(P1)305]. In the PE spectrometer **23** is stable up to  $250^\circ\text{C}$  (93CB2675). The dispirothiirane was identified in the pyrolysis mixture by comparison with the PE spectra of a pure sample recorded at different temperatures.



The pyrolytic reaction of 1,5,5-trimethyl-4-phenyl-4,5-dihydro-1*H*-tetrazole (**24**), which differs from that of other tetrazolines (see Section V.D), certainly has to be associated with the *N*-phenyl group (88CB1213). It is well known that tetraaryl-2-tetrazenes are considerably less stable than the corresponding alkyl compounds (84MI2). Accordingly, the two N-N single bonds in **24** can be expected to differ in strength. The initial step is the scission of the N-N bond between the *N*-phenyl and the azo groups. Homolysis of this bond will be favored through stabilization of the aminyl

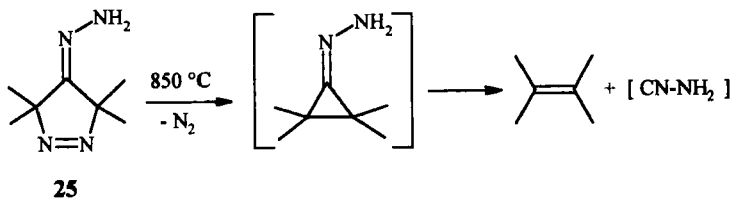
<sup>3</sup> Ring contraction of heterocycles by sulfur extrusion including a chapter on "four-membered rings from five-membered rings" was recently reviewed by Bohle and Liebscher [96AHC(65)39].



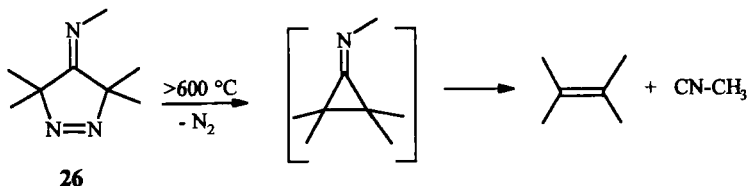


radical by the phenyl group. The resulting 1,5-diradical will lose molecular nitrogen, leading to a 1,3-diradical that will recombine to give the diazirine. A similar stepwise mechanism has been discussed by Gowenlock *et al.* (63CJC1911) for the decomposition of acyclic 2-tetrazenes.

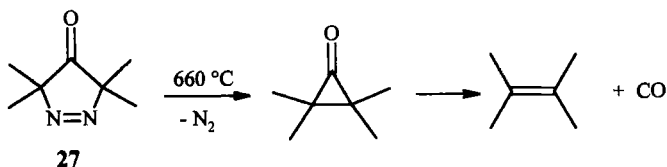
Compounds with an exocyclic double bond on C-4 that also undergo ring contraction are the pyrazolin-4-one hydrazone **25** (96T1965), the 4-(methylimino)pyrazoline **26** (90CB1161), and the pyrazolin-4-one **27** (90CB1161). In most cases the corresponding cyclopropane derivatives are unstable or semistable and decompose into an alkene and other small molecules such as *iso*-cyanamide and carbon monoxide. In the pyrolysis of **25**, 2,3-dimethyl-2-butene is observed, indicating that ring contraction must take place (96T1965). There are, however, also other ways of decomposition.



The imine **26** shows a similar behavior (90CB1161). In this case, too, the reaction products (2,3-dimethyl-2-butene and methyl isocyanide) are the expected thermolysis products of a cyclopropane derivative, and it is therefore safe to postulate the latter as the ring contraction product that is formed by cyclization of an intermediate diradical evolving from **26**.

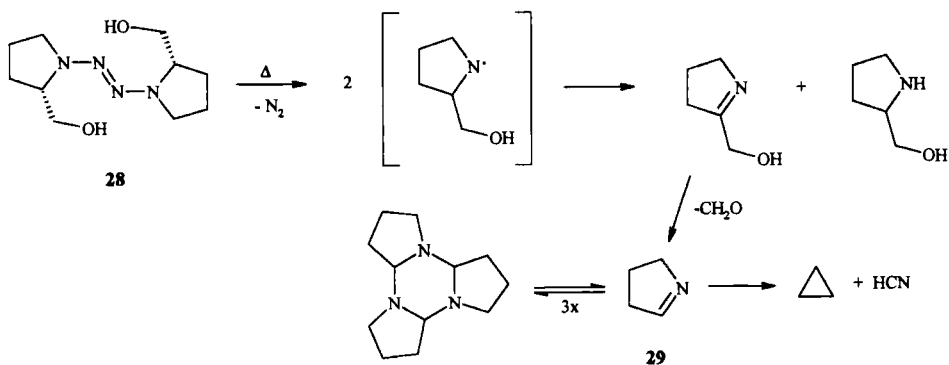


Pyrolysis and photolysis of the dihydropyrazolone **27** have been investigated by several groups with different techniques, and different pathways of decomposition have been found [74CJC4040; 81AG293, 81AG(E)291,



81JA998]. Under FVP conditions the main reaction is ring contraction to semistable 2,2,3,3-tetramethylcyclopropanone (90CB1161).

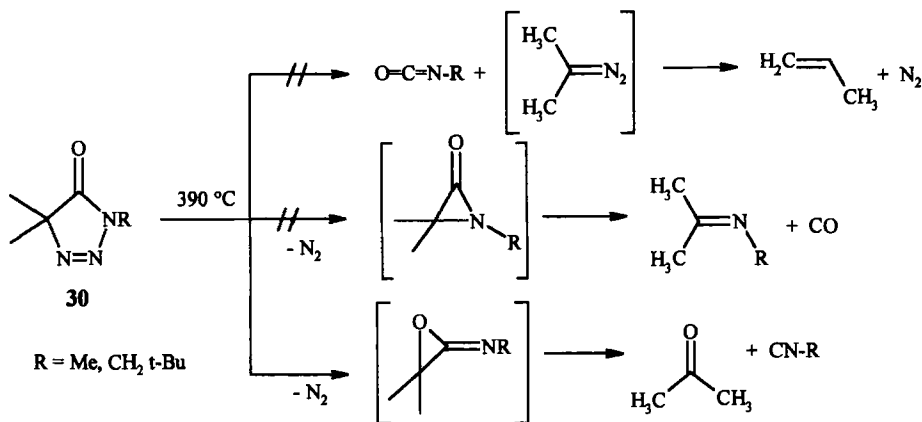
Small stable molecules other than  $N_2$ , such as HCN or  $C_2H_2$ , may be ejected from a five-membered ring compound, leading to ring contraction. However, only a few examples are known. The decomposition of 1-pyrroline (3,4-dihydro-2*H*-pyrrole, **29**) affording cyclopropane and hydrogen cyanide was discovered in a PES thermolysis study of the chiral hydroxyalkyl-2-tetrazene (*S,S*)-1,2-bis[2-hydroxymethyl]pyrrolidino]diazene (**28**) in which **29** is an intermediate (97UP1); **29** trimerizes to the corresponding hexahydro-1,3-5-triazin, from which it can be generated thermally through [2 + 2 + 2]-cycloreversion (86CB554; 87CB197).



## B. RING CONTRACTION (NON-LEAST-MOTION PATH)

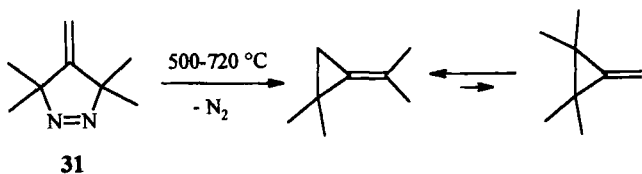
Ring contraction by the non-least-motion path requires the intermediate formation of an acyclic species that is able to undergo structural changes that finally provide a new three-membered ring in which a formerly exocyclic atom has moved to a ring position. An explanation of this behavior is not always simple (discussed later) because unexpected products may

also be formed. However, in most cases the observed products allow a conclusion about the nature of this new intermediate ring compound, although it may be too unstable to be directly detected. A typical example is the thermolysis of trialkyl-substituted 3,5-dihydro-4*H*-1,2,3-triazol-4-ones (**30**). In analogy to photolysis and solution thermolysis (87CB217,225), three reaction paths can be formulated. Because molecular nitrogen, acetone, and the alkyl isonitrile are the only detected products, paths other than that involving the imino oxirane intermediate can be excluded (93CB2683). It is rather surprising that the path via the  $\alpha$ -lactam is not followed. This question of selectivity in non-least-motion ring contractions is addressed in Section V.C.

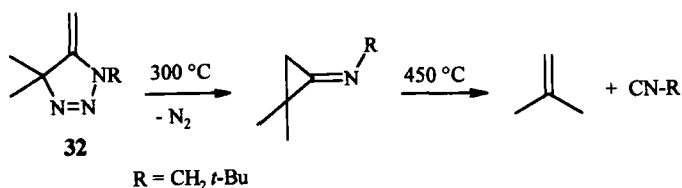


Following Crawford's pioneering search for trimethylenemethane in the pyrolysis of 4,5-dihydro-4-methylene-3*H*-pyrazole (65JA3023; 66JA2589), the thermolyses of numerous 4-alkylidene-3,5-dihydro-4*H*-pyrazoles have been investigated (74CJC4033; 80CRV99; 86JA1019). The thermal extrusion of molecular nitrogen from such compounds has also been the subject of theoretical studies (79JA2269).

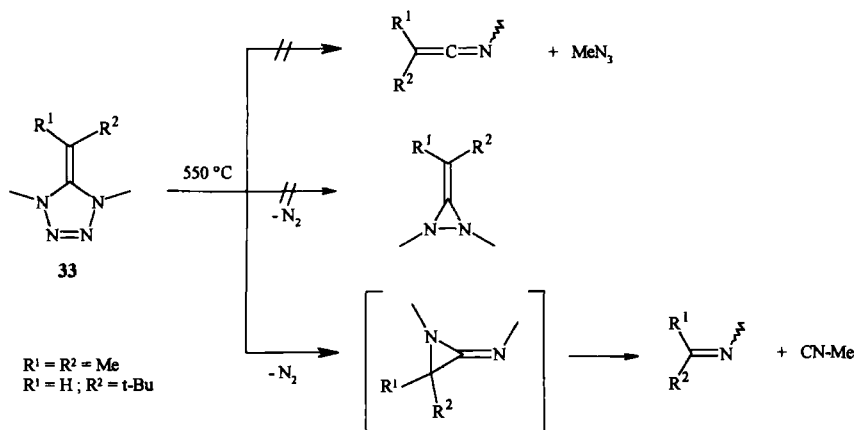
In the gas-phase pyrolysis of dihydro-3,3,5,5-tetramethyl-4-methylene-4,5-3*H*-pyrazole (**31**), only 1-isopropylidene-2,2-dimethylcyclopropane was found; it is stable under the reaction conditions as the only product in addition to molecular nitrogen (90CB1161). If thermodynamic product control is assumed, which seems reasonable in view of the high temperature, then the exclusive observation of the non-least-motion product is readily explained in terms of the low equilibrium concentration of its isomer, which is below the limit of detection by PE spectroscopy.



Photolysis of 1-(2,2-dimethyl-propyl)-4,4-dimethyl-5-methylene-4,5-dihydro-1*H*-1,2,3-triazole (**32**) and its thermolysis in solution at 70°C afford, besides molecular nitrogen, diastereoselectively (*E*)-*N*-(2,2-dimethyl-propyl)-2,2-dimethylcyclopropane imine, which decomposes thermally at 150°C or under irradiation with light of short wavelength to 2-methylpropene and dimethylpropylisocyanide (87CB1049). FVP/PES studies confirmed these results, indicating a single mechanism for the decomposition of this compound (93CB2683).

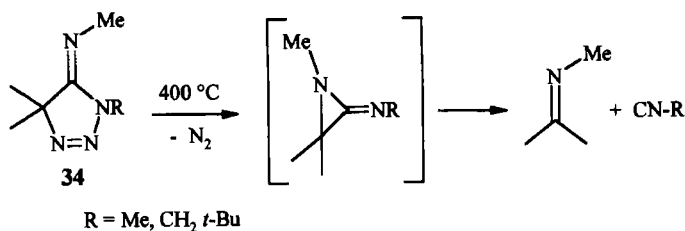


For 5-alkylidenetetrazolines (**33**) three reaction paths have to be considered. They afford either *N*-methyl ketene imines and methyl azide, or, in addition to molecular nitrogen, a 3-alkylidenediaziridine (least-motion path) or a methyliminoaziridine (non-least-motion path). As was shown by

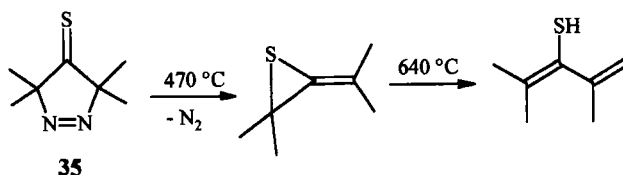


FVP/PES, only the last-mentioned path is followed (92TH1). This is proven by the formation of an imine and methylisocyanide, a process that can only be explained with the aziridine derivative as an intermediate that suffers retrocycloelectronic splitting.

In the photolysis of methyl-(3,5,5-trialkyl-3,5-dihydro-[1,2,3]triazol-4-ylidene)-amine (**34**) in solution, aziridine imines are formed quantitatively, about 85% on the non-least-motion path and 15% on the least-motion path (90CB2195). The gas-phase pyrolysis of **34** affords only the product of the former path (93CB2683).

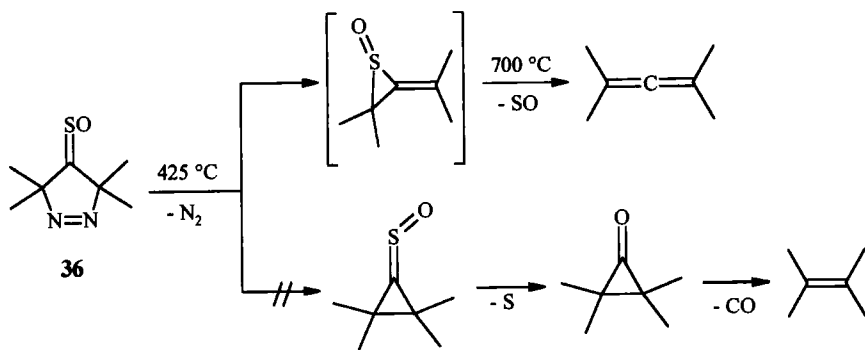


Photolysis and thermolysis in solution of 3,5-dihydro-3,3,5,5-tetramethyl-4H-pyrazole-4-thione (**35**) have been investigated by Quast and Fuss [81AG293, 81AG(E)291]. Photoextrusion of molecular nitrogen from **35** affords 3-isopropylidene-2,2-dimethylthiirane as the only product, which is also formed thermally with a yield of 40% in benzene solution at 141°C. Higher yields are precluded by the thermal instability of the product. In the PES-controlled gas-phase pyrolysis of **35**, the thiirane is observed to isomerize at higher temperatures to 2,4-dimethyl-1,3-pentadiene-3-thiol (90CB1161). The latter dienethiol has been reported as the only product formed in the FVP of **35** and from the thiirane (86T5301, 86TL4035).



Irradiation of 3,5-dihydro-3,3,5,5-tetramethyl-4H-pyrazole-4-thione *S*-oxide (**36**) in benzene- $d_6$  solution with light of wavelengths above 320 nm affords predominantly tetramethylallene and tetramethylpyrazolinone (**27**) (3:2) together with small amounts of a third product characterized by a 2,4-dimethylpenta-1,3-dien-3-yl moiety as shown by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (92TH2). The photolysis of similar pyrazolinethione *S*-oxides in solution has been investigated by Schaumann *et al.* (81T219), who have studied com-

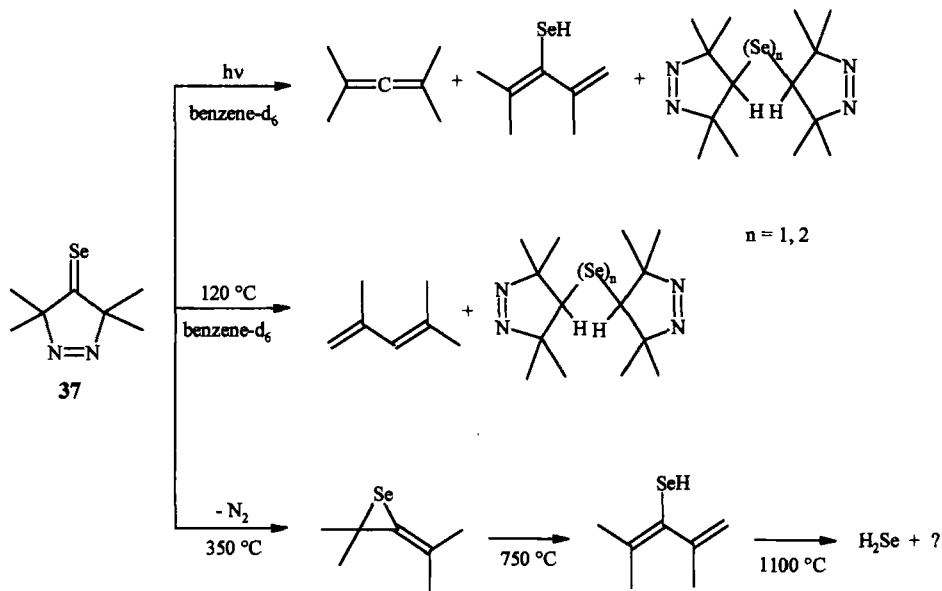
pounds bearing two methyl groups at C-5 and two tertiary alkyl groups at C-3 of the pyrazoline ring. These pyrazolinethione *S*-oxides are reported to lose nitrogen to form alkylidenethiirane *S*-oxides in low yields. On thermolysis, thiirane *S*-oxides are known to eliminate sulfur monoxide, which is highly unstable and eventually yields sulfur dioxide [65AG437; 87AG101, 87AG(E)98]. Other thione *S*-oxides, including the parent sulfine, thioformaldehyde *S*-oxide, decompose via intermediate oxathiiranes, which eliminate elemental sulfur to produce the corresponding aldehyde or ketone (76JA1264; 91TL747). This mechanism accounts for the formation of tetramethyl-dihydropyrazolone (**27**) in the photolysis of **36**. The results of *ab initio* calculations at the MP-2 level by Block, Schwan, and Dixon (92JA3492) show that the isomers 3,3-dimethyl-2-isopropylidenethiirane *S*-oxide and tetramethylcyclopropanethione *S*-oxide are essentially isoenergetic, the former being more stable than the latter by as little as  $1.7 \text{ kJ} \cdot \text{mol}^{-1}$  after zero-point corrections.



By PE spectroscopic analysis of the gas-phase pyrolysis, it was shown that the decomposition of thione *S*-oxide **36** occurs in two steps (96T1965). The expected band of sulfur dioxide (12.64 eV) is observed at 700°C, whereas no ionization bands belonging to sulfur monoxide are detected. In the low-energy region of the spectrum, bands at 8.52 and 9.00 eV belonging to tetramethylallene are observed. This is the expected product for loss of sulfur monoxide from the alkylidenethiirane *S*-oxide, which may result from the extrusion of dinitrogen from the sulfine (**36**). The alternative primary product would be the tetramethylcyclopropanethione *S*-oxide. This hypothetical species is expected to decompose into sulfur and tetramethylcyclopropanone, and hence should provide the same pyrolysis PE spectrum as that from tetramethyl-dihydropyrazolone (**27**) (90CB1161), the most prominent feature of which (except for the bands of molecular nitrogen) is the ionization band of carbon monoxide at 14.01 eV. Because this band is

missing in the high-temperature pyrolysis PE spectrum of **36**, the intervention of tetramethylcyclopropanone, and therefore tetramethylcyclopropanethione *S*-oxide, as an alternative primary decomposition product is excluded.

Because only a small number of stable selenoketones exist, studies of their decomposition are scarce. Irradiation of di-*tert*-alkylselones with UV light in hydrogen-donating solvents affords diselenides (80CJC6; 87MI1), and the selone **37** behaves likewise. A second path of photolysis involves extrusion of molecular nitrogen from **37** to yield eventually tetramethylallene and elemental selenium, probably via the elusive 3,3-dimethyl-2-isopropylideneselenirane. This hypothesis is corroborated by the observation of additional products that are derived from 2,4-dimethylpenta-1,3-diene-3-selenole. Heating a solution of **37** in benzene- $d_6$  to 120°C leads to a similar mixture of products, except that 2,4-dimethylpentadiene, which apparently arises from tetramethylallene by an acid-catalyzed rearrangement, predominates (68JOC4080). Thus, attempts to observe the alkylideneselenirane in solution have been frustrated by its instability in the condensed phase (92TH2).



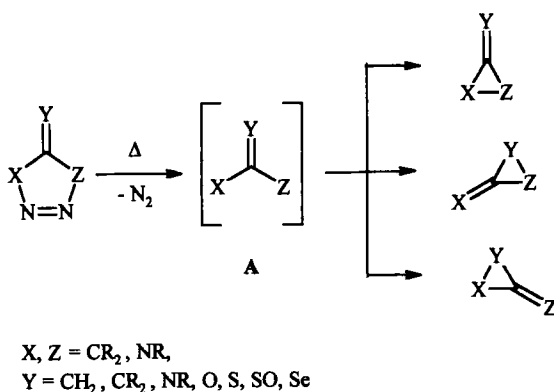
The photochemical properties of selenoketones resemble those of thioketones rather than ketones (80CJC6; 87MI1). This also holds for their electronic structures (96T1965). Therefore, it was not surprising to observe an analogy between the gas-phase pyrolysis of selone **37** (96T1965) and that of the corresponding thione **35** (90CB1161). In both cases, three steps

can be distinguished. At 350°C, the elimination of molecular nitrogen from **37** leads to the non-least-motion product (i.e., the novel isopropylideneselenirane). Surprisingly, this does not lose selenium (87MI2) at 750°C but rearranges to form the selenole, which decomposes into hydrogen selenide and unidentified products at 1100°C. As an independent structural proof for the selenirane, it was studied by IR spectroscopy at low temperature in an argon matrix (96T1965). In this experiment, the selenirane was generated from **37** by photolysis in the matrix and by gas-phase thermolysis at temperatures between 350 and 800°C. As expected, the IR spectrum resembles that of the corresponding thiirane, and the observed frequencies and intensities are in good agreement with those obtained by *ab initio* calculations.

### C. SELECTIVITY IN RING CONTRACTION REACTIONS

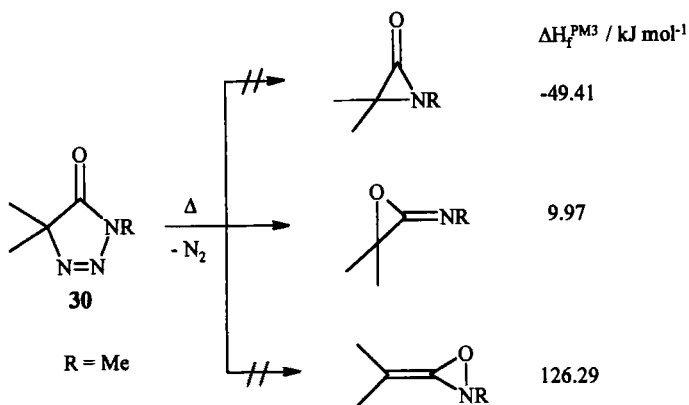
As mentioned earlier,  $[5 \rightarrow 3 + 2]$  ring contraction of a five-membered ring compound with an exocyclic double bond can lead to a three-membered ring either on the least-motion or on the non-least-motion path. In the most general case, three different products are possible; one is formed directly on the former and two can be formed indirectly on the latter path. We have investigated the relevant question of selectivity in some detail (92TH1).

The intermediate **A** may be an 1,3-diradical or another reactive species.



If it is a real intermediate and not too short-lived, it is likely that the thermodynamically most stable product will be formed, and this seems to be the usual case. Examples are found in the decompositions of **25–27**, which follow the least-motion path, and **31–37**, which follow the non-least-motion path. The most obvious exception is the triazolinone system **30** (Scheme 1).





SCHEME 1

Heats of formation have been calculated by the PM3 method (89MI1) for the three possible isomeric products; only that with the medium  $\Delta H_f$  value is observed and not the most stable  $\alpha$ -lactam. These findings cannot be explained with an intermediate species like **A**. An interpretation is, however, possible based on PM3 calculations for the energy hypersurface of this reaction (92TH1).  $\Delta H_f$  values were calculated as a function of bond distances N-1-C-5 and N-2-N-3, the results are depicted in Fig. 1. With this diagram, the

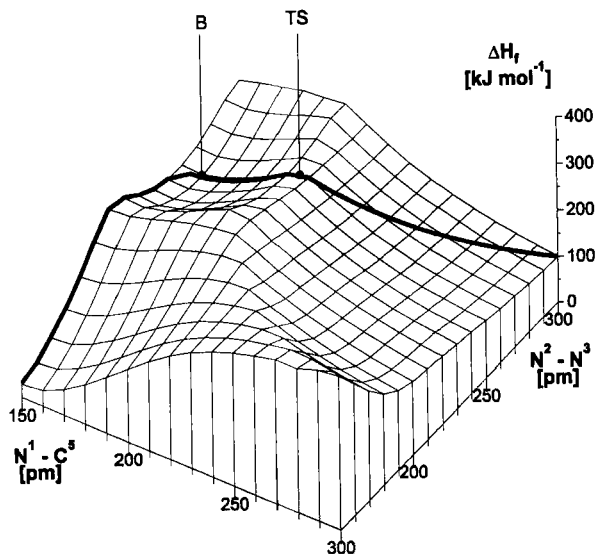


FIG. 1. Potential energy hypersurface for the fragmentation of triazolinone **30** (92TH1).

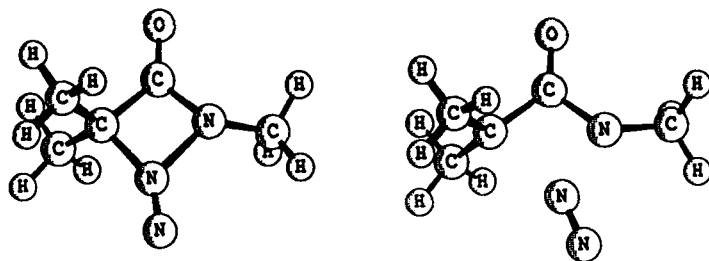


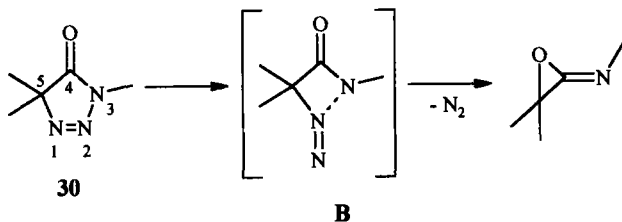
FIG. 2. Structures of intermediate **B** and transition state **TS** for its decomposition (PM3 results) (92TH1).

fragmentation of **30** ( $R = \text{Me}$ ) can be described as a two-step mechanism. In the first step, the weakest bond of the ring (N-2-N-3) is cleaved, and an intermediate **B** with a four-membered ring is formed that has a N-1-N-3 distance of 169 pm. In the second step, the N-1-C-5 bond is split and simultaneously the new ring bond between C-5 and O is formed. In Fig. 2 structures corresponding to selected points of the diagram shown in Fig. 1 are depicted.

A proof for this mechanisms might be obtained with a chiral triazolinone in which C-5 would be an asymmetric center. Inversion of its configuration would be consistent with the proposed two-step mechanism in which **B** would be an intermediate (Scheme 2). If the reaction followed the general path with **A** being an intermediate, the reaction should not be stereospecific and racemization of C-5 should be observed.

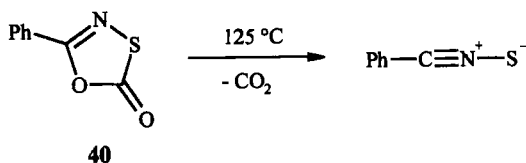
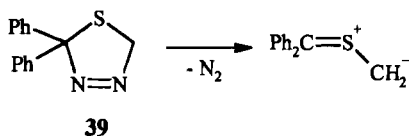
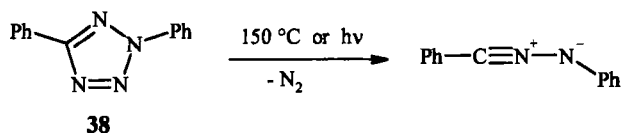
#### D. $[5 \rightarrow 3 + 2]$ CYCLOREVERSION

1,3-Dipolar cycloaddition (84MI5) is an important synthetic method to prepare five-membered heterocycles. As a  $[4\pi + 2\pi]$  pericyclic reaction it is allowed, according to orbital symmetry, to be concerted. The same holds for the inverse reaction, 1,3-dipolar cycloreversion [79AG781, 79AG(E)721; 84MI3], leading to a  $[5 \rightarrow 3 + 2]$  fragmentation of the ring, and indeed many 1,3-dipoles used as reagents in cycloadditions are generated by cyclorever-

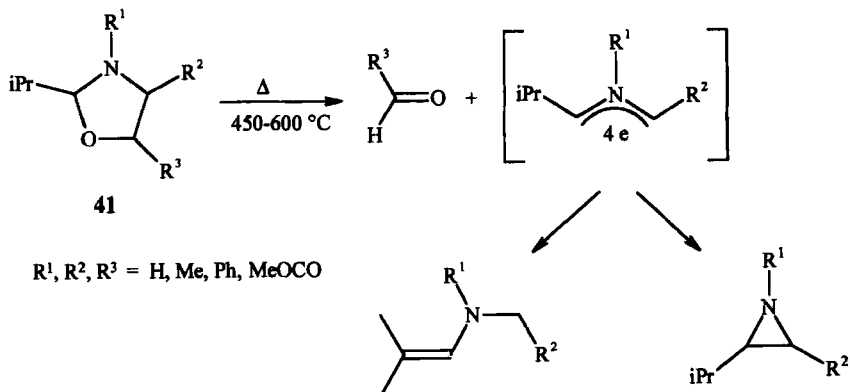


SCHEME 2

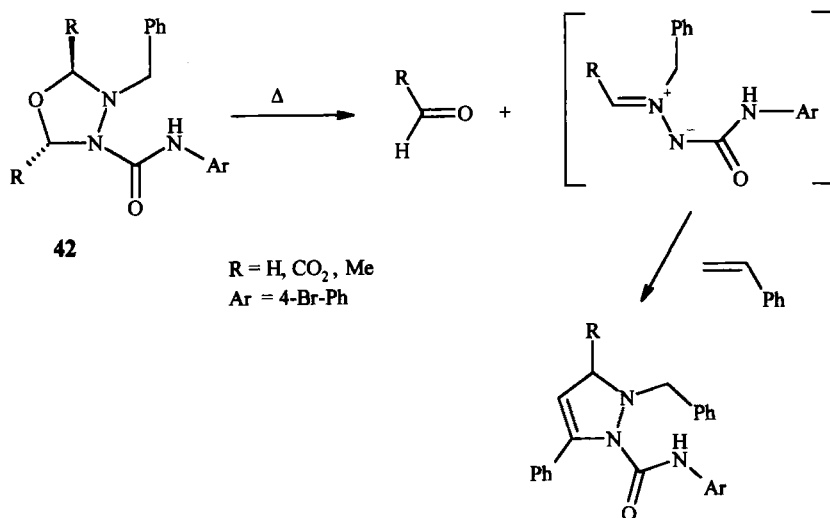
sion. Typical examples are the fragmentations of 2,5-diphenyltetrazole (**38**), 2,2-diphenyl-1,3,4-thiadiazoline (**39**), and 5-phenyl-1,3,4-oxathiazolin-2-one (**40**), by which a nitrilimine, a thiocarbonyl ylide, and a nitrile sulfide, respectively, are produced (84MI4). When the 1,3-dipolar species generated in this reaction cyclizes to a three-membered ring, the overall reaction is a ring contraction, and several examples mentioned in Section V.A follow this mechanism.



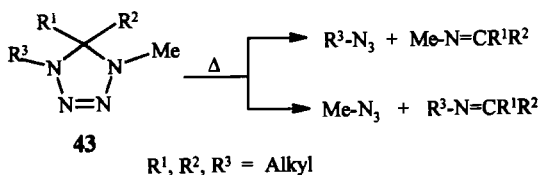
Azomethine ylides can be generated from oxazolidines in the liquid phase by thermolysis and in the gas phase by FVP (90TL6017; 92T8947). Depending on the other substituents and the FVP conditions, from 2-isopropoxyloxazolidines (**41**) either aziridines or enamines, or a mixture of them, are obtained by ring closure or hydrogen shift of the azomethine ylide.



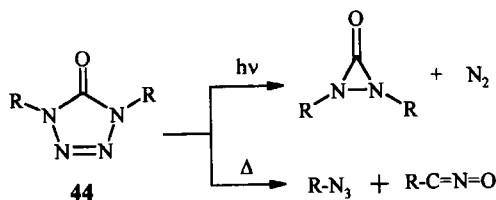
Azomethine imines were generated by cleavage of certain 1,3,4-oxadiazolidines (**42**) and subsequently trapped with dipolarophiles such as styrene and stilbene affording pyrazolidine heterocycles (96TL4323).



Typical 1,3-dipolar cycloreversion is found for the decomposition of alkyl-substituted 2-tetrazolines (**43**) (88CB1213), 1,4-dihydro-1,2,3,4-tetrazol-5-ones (**44**), and -thiones (**45**) (97JHC113). For these reactions two paths are possible that can be distinguished when the substituents on N-1 and N-4 are different. For 2-tetrazolines ring contraction leading to diaziridines is also possible (discussed earlier). Cycloreversion of **43** yields imines and azides (88CB1213).



For the thermolysis of tetrazolinones (**44**), ring contraction leading to diaziridinones has to be considered as an alternative decomposition path. This was actually observed by Quast *et al.* [75AG422, 75AG(E)428; 81CB325; 85CB526; 89T259] in the photolysis of the 1,4-dimethyl derivative **44e** and other alkyl-substituted tetrazolinones. The photolysis of phenyl-substituted compounds **44d** and **44f** yields benzimidazolones, and electron-

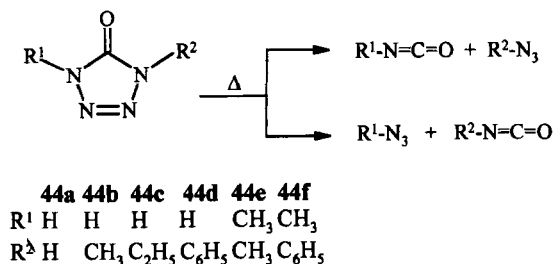


impact-induced decomposition was found to proceed via  $[5 \rightarrow 3 + 2]$  cycloreversion to azides and isocyanates.

In the gas-phase thermolysis of **44**, only the products of cycloreversion are observed (97JHC113). The unsymmetrically substituted compounds **44c** and **44d** seem to decompose by the two alternative ways, because both isocyanic and hydrazoic acid are detected simultaneously. However, from the complementary products only ethyl and phenyl isocyanate, but not the corresponding azides, are found. Compounds **44b** and **44f** decompose only in one way, affording methyl isocyanate and hydrazoic acid, and phenyl isocyanate and methyl azide, respectively, as the primary reaction products (Scheme 3).

For the selectivity observed in the fragmentation of some of the compounds, either thermodynamic or kinetic effects are responsible (97JHC-113). Neglecting entropic effects because these parameters are not known, from the experimental enthalpies of formation it follows for **44b** that the decomposition products  $\text{HN}_3 + \text{CH}_3\text{NCO}$  are favored by  $47.3 \text{ kJ} \cdot \text{mol}^{-1}$  over their counterparts  $\text{CH}_3\text{N}_3 + \text{HNCO}$ . This is in accord with the experimental findings. For the fragmentation of **44f**, however,  $\text{PhN}_3 + \text{CH}_3\text{NCO}$ , and not  $\text{CH}_3\text{N}_3 + \text{PhNCO}$ , should be expected, owing to an enthalpy difference  $\Delta\Delta H_f$  of  $157.8 \text{ kJ} \cdot \text{mol}^{-1}$ , which contradicts the experiment.

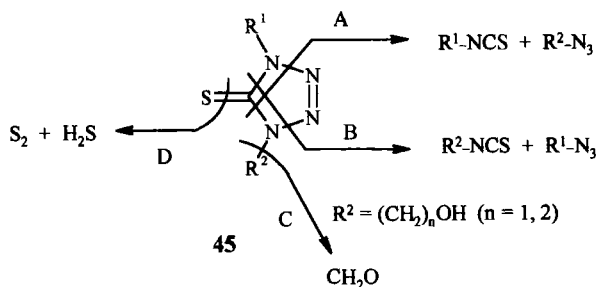
The kinetic aspects of these reactions were inspected by the frontier molecular orbital (FMO) method for the 1,3-dipolar cycloaddition reactions of  $\text{R}^1\text{N}_3 + \text{R}^2\text{NCO}$  or  $\text{R}^2\text{N}_3 + \text{R}^1\text{NCO}$  affording the corresponding tetrazolinone (97JHC113). Making use of the Klopman-Salem equation, from



SCHEME 3

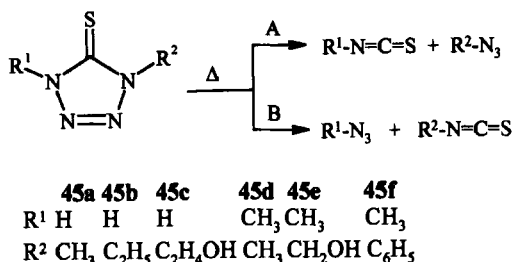
the energies of the highest occupied and the lowest unoccupied molecular orbitals (HOMOs and the LUMOs), and the orbital coefficients on the respective atoms of the reactants, the energies  $S$  associated with the interactions of the FMOs were estimated:  $\text{HN}_3 + \text{CH}_3\text{NCO} \rightarrow \mathbf{44b}$  ( $S = 0.135$ ),  $\text{CH}_3\text{N}_3 + \text{HNCO} \rightarrow \mathbf{44b}$  ( $S = 0.135$ );  $\text{PhN}_3 + \text{CH}_3\text{NCO} \rightarrow \mathbf{44f}$  ( $S = 0.097$ ),  $\text{CH}_3\text{N}_3 + \text{PhNCO} \rightarrow \mathbf{44f}$  ( $S = 0.151$ ). Only in the second case is a clear distinction possible with the  $S$  values: the latter reaction is predicted to be faster than the former. Under the assumption that cycloaddition and cycloreversion have identical transition states, the same should hold for the decomposition of  $\mathbf{44f}$  into  $\text{CH}_3\text{N}_3$  and  $\text{PhNCO}$ , which indeed is observed. It can thus be concluded that the thermolytic fragmentation of tetrazolinone  $\mathbf{44f}$  is a kinetically controlled reaction, whereas the fragmentation of  $\mathbf{44b}$  and the other aliphatic tetrazolinones probably is thermodynamically controlled. The question of why these tetrazolinones should behave in different manners remains to be answered.

There are several possible routes (paths A–D) for the thermolysis of tetrazolinethiones ( $\mathbf{45}$ ) to take place [75AG422, 75AG(E)428; 81CB325; 85CB526; 89T259]: (A) and (B) 1,3-dipolar cycloreversion affording isothiocyanates and azides, (C) cleavage of functionalized substituents, and (D) cleavage of sulfur.



Path D, followed by  $\text{N}_2$  extrusion affording carbodiimides, was revealed as the main route for photolysis of tetrazolinethiones [75AG422, 75AG(E)428; 81CB325; 85CB526; 89T259]. However, cycloreversion to isothiocyanates and azides (paths A and B) was observed as the main mechanism in the fragmentation under mass spectrometric conditions (electron impact ionization). Most of the compounds  $\mathbf{45}$  decompose thermally in more than one way (97JHC113):  $\mathbf{45a-d}$  are cleaved through cycloreversion (paths A and B) and the elimination of sulfur (path D), which is followed by cycloreversion of the remaining ring (Scheme 4).

In a uniform reaction,  $\mathbf{45f}$  undergoes cycloreversion to phenyl isothiocyanate and methyl azide (path B). The products corresponding to path A



SCHEME 4

are not observed, and **45f** is the only case in which no sulfur (S<sub>2</sub>) and hydrogen sulfide are formed. Methyl and ethyl isothiocyanate are generated together with hydrazoic acid from **45a** and **45b**, respectively, on path B, and simultaneously methyl and ethyl azide are formed, although in minor amounts, on path A. **45e** is unstable even at about 35°C and loses formaldehyde (path C), affording **45a**, which decomposes at higher temperatures (>600°C) as discussed earlier.

Sulfur is observed as a dimer (S<sub>2</sub>), the most stable modification under FVP/PES conditions [65AG437; 87AG101, 87AG(E)98]. It is always accompanied by hydrogen sulfide. This is evidence that sulfur is cleaved as a free atom that dimerizes or abstracts two hydrogen atoms forming H<sub>2</sub>S. There are two further indications for path D as an independent route for the decomposition of tetrazolinethiones:

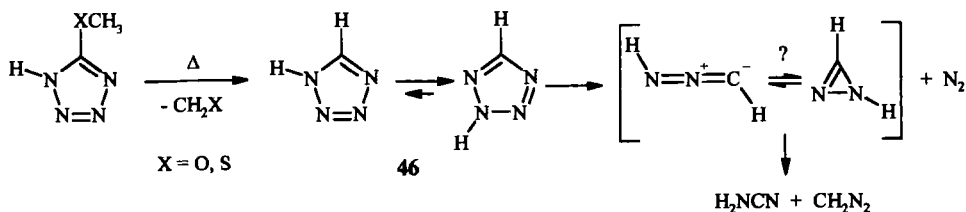
- Methyl isonitrile that is identified in the pyrolysis mixtures of **45d** and **45e** can only be formed *after* sulfur has been split off.
- Most probably sulfur is not cleaved from the products *after* cycloreversion, because methyl, ethyl, and phenyl isothiocyanate are stable under the pyrolysis conditions.

There is no indication of the formation of dimethyl carbodiimide or methyl phenylcarbodiimide as in the photolysis of **45d** and **45f** [75AG422, 75AG(E)428; 81CB325; 85CB526; 89T259], respectively, in the PE spectra of the pyrolysis mixtures (97JHC113).

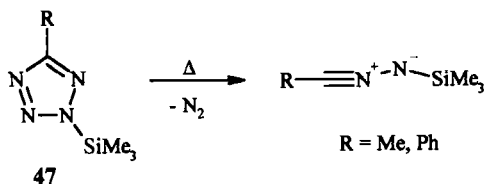
The main difference in the thermolysis of tetrazolinones (**44**) and tetrazolinethiones (**45**) is the generation of sulfur (S<sub>2</sub>) and hydrogen sulfide from the latter compounds. The sulfur atom is split off from the starting molecules and not from a thermolysis product such as an isothiocyanate in a secondary reaction. The sulfurless tetrazole is then cleaved by cycloreversion, affording the corresponding isonitrile as a product that cannot be explained otherwise. There is little in common between photolysis and thermolysis of

tetrazolinones **44** and tetrazolinethiones **45**; only elemental sulfur is generated by both methods from the latter compounds. On the other hand, largely the same products are formed by thermal and by electron-impact-induced decomposition.

5-Methoxy- and 5-methylthiotetrazole lose formaldehyde and thioformaldehyde, respectively, affording unsubstituted tetrazole (**46**), which decomposes mainly through extrusion of nitrogen and formation of cyanamide and diazomethane (89CP157; 97JHC113), both probably formed through isodiazirine (89CP157), making the classification of this reaction as either  $[5 \rightarrow 3 + 2]$  cycloreversion or ring contraction difficult. Matrix photolysis (80C504,506; 80JA2093) and FVP [85AG74, 85AG(E)56; 87TL617] of 2,5-disubstituted tetrazoles cause elimination of molecular nitrogen and formation of nitrilimines. For the parent compound, unsubstituted tetrazole (**46**), FVP studies at 800°C and photolysis in cryogenic matrices in combination with IR spectroscopy were recently reported by Maier and co-workers (96LA1041) who found nitrilimine, HCNNH, as a product in both fragmentations.

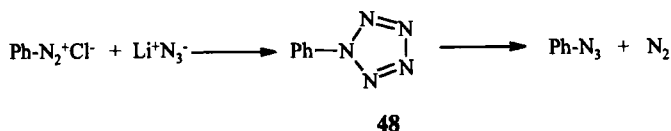


Gas-phase thermolysis of 5-methyl- and 5-phenyl-2-(trimethylsilyl)-tetrazole (**47**) has been studied by real-time PE spectroscopy by Bock *et al.* (87TL617).  $\text{N}_2$  is split off quantitatively at the spectroscopically optimized temperatures of 750 K ( $\text{R} = \text{CH}_3$ ) and 770 K ( $\text{R} = \text{C}_6\text{H}_5$ ), and the substituted nitrile imines are generated exclusively.



In this review, at least briefly, the “classical” investigation of Huisgen and Ugi [56AG705; 57CB2914; 64AHC(3)373; 93AG242, 93AG(E)230] on phenylpentazole (**48**) has to be mentioned. **48** was generated from benzene diazonium chloride and lithium azide as an unstable compound that

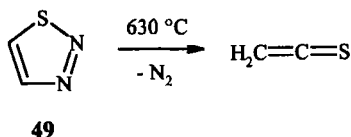




decomposes to phenyl azide and dinitrogen in a 1,3-dipolar cycloreversion.

In the thermal decomposition of 2,3-dihydrofuran (**9**), [5 → 3 + 2] fragmentation to ketene and ethene occurs as the minor reaction (89JPC1139). The main reaction is a [5 → 5] isomerization (see Section III) (Scheme 5).

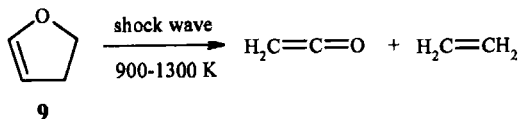
The unstable compound thioketene can be generated from 1,2,3-thiadiazole (**49**) by gas-phase pyrolysis (77JA1663).



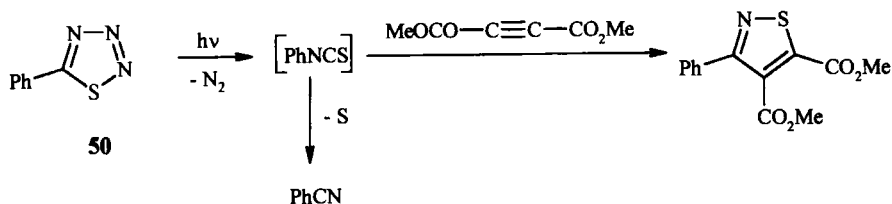
### E. OTHER [5 → 3 + 2] FRAGMENTATIONS

Phenyl isothiocyanate (benzonitrile sulfide) is formed photolytically from 5-phenyl-1,2,3,4-thiadiazole (**50**) and related heterocycles (**51**) when extrusion of a small inorganic fragment such as N<sub>2</sub>, CO, CO<sub>2</sub>, COS, or CS<sub>2</sub> is possible [78JCS(P1)1445]. Rapid decomposition to benzonitrile takes place at room temperature, but the sulfide may be trapped as a cycloaddition product by carrying out the photolysis in neat dimethyl acetylenedicarboxylate. Among the compounds that have been studied are 5-phenyl-substituted 1,3,4-oxathiazol-2-one (**51a**), 1,3,4-dithiazol-2-thione (**51b**), 1,3,4-oxathiazol-2-thione (**51c**), 3,1,4-oxathiazol-2-one (**51d**), and meso-ionic 3,1,2-oxathiazol-2-one (**51e**) (Scheme 6).

Tetrahydrofuran (THF, **52**) is a very stable five-membered ring ether. The thermal decomposition of THF was studied in a heated bulb over the temperature range 530–670°C (46JA506; 51JA175) and behind reflected shocks in a single-pulse shock tube over the temperature range 1070–1530 K



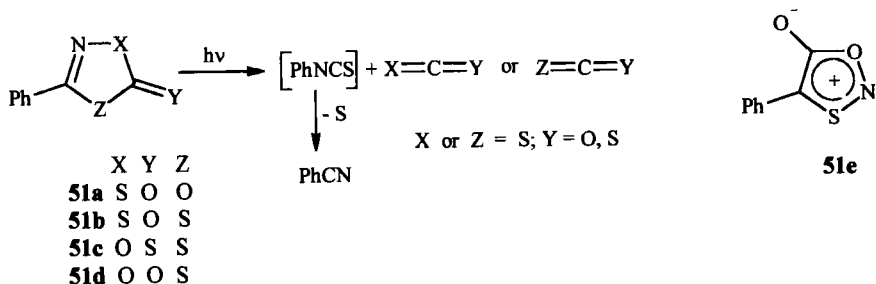
SCHEME 5



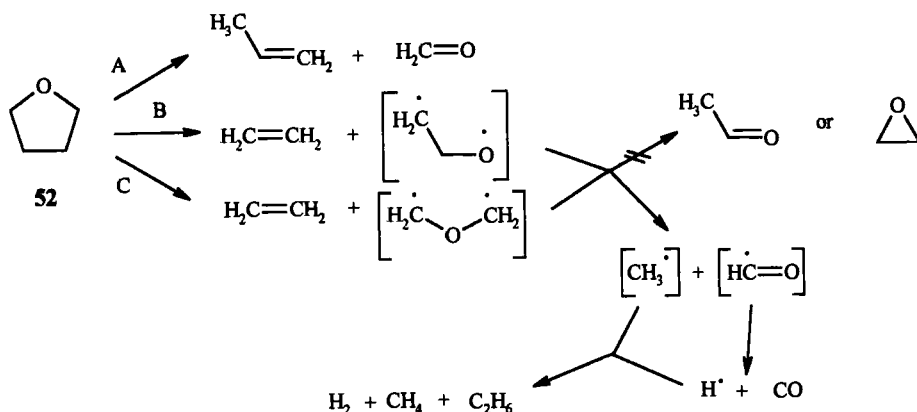
(86JPC3422). Many different products were found in both studies, which agree insofar as the five-membered ring suffers  $[5 \rightarrow 3 + 2]$  fragmentation in two different ways, affording either  $\text{CH}_2\text{O} + \text{C}_3\text{H}_6$  (path A) or  $\text{C}_2\text{H}_4 + \text{C}_2\text{H}_4\text{O}$  (paths B and C). In the former study, it was concluded that the  $\text{C}_2\text{H}_4\text{O}$  fragment isomerizes to acetaldehyde, but in the latter investigation it was shown that this residue isomerizes to neither acetaldehyde nor oxirane but dissociates to methyl and formyl radicals, producing carbon monoxide as the only oxygenated product of paths B and C. In path A, which is also the main reaction route on electron impact ionization, propene and formaldehyde are formed. The production of ethene was found to be approximately four times faster than the production of propene.

In the shock tube investigation of **52**, a series of experiments was performed using mixtures of THF and THF- $\text{d}_8$  and also partially deuterated (3,3,4,4- $\text{D}_4$ ) reactant, which enabled clear conclusions with regard to the cleavage of individual bonds. In this way it was shown that ethene is formed by elimination from the THF ring at the C-2-C-3 (C-4-C-5) (path B) and C-3-C-4 positions (path C) in a ratio of  $\approx 2.2:1$ , which indicates that the rates of these paths are practically identical except for the statistical factor of 2.

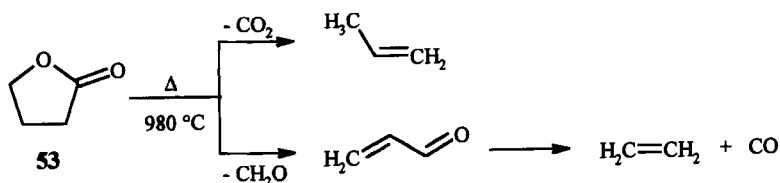
$\gamma$ -Butyrolactone (**53**) has a good leaving group ( $\text{CO}_2$ ) performed in the molecule, and one can expect a much easier and less complicated fragmentation than that of THF (**52**). Pyrolysis of esters is a standard method for the



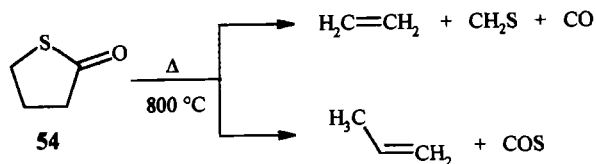
SCHEME 6



generation of C–C double bonds, and commonly esters are cleaved to afford an alkene and a carboxylic acid. Lactones of ring size larger than six atoms pyrolyze in a similar way at about 520°C to yield an unsaturated acid (77JOC3895). Pyrolysis of **53** was investigated under FVP conditions, and the products were detected by PE spectroscopy [93JCS(P2)1249]. Decarboxylation with the formation of propene is the major mode of decomposition. The reaction probably proceeds through the formation of a trimethylene diradical that rearranges to give propene. The formation of cyclopropane as another intermediate that would isomerize to propene under the reaction conditions cannot be ruled out. The reaction is thus related to the pyrolysis of pyrazoline (**2**), which requires, however, a considerably lower temperature (400°C), at which cyclopropane is formed. A minor mode of decomposition for **53** leads to another [5 → 3 + 2] fragmentation by which acrolein and formaldehyde are produced. Most of the acrolein decomposes into ethene and carbon monoxide. Both types of fragmentation of **53** are also induced by electron impact ionization.

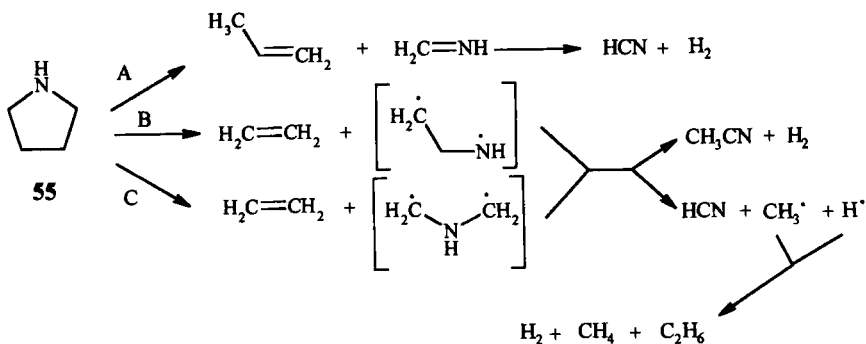


The fragmentation of  $\gamma$ -thiobutyrolactone (**54**), studied by the same technique as that for **53**, also shows two main paths of decomposition [93JCS(P2)1249]. However, in this case decarboxylation with simultaneous formation of ethene and thioformaldehyde ([5 → 2 + 2 + 1] fragmenta-

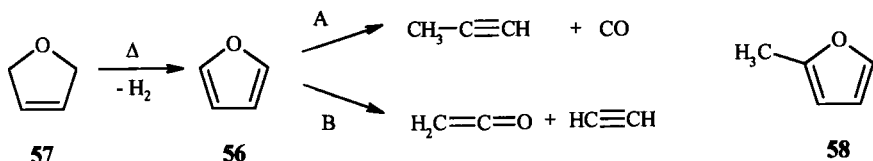


tion) is the major mode and cleavage into COS and propene is the minor mode.

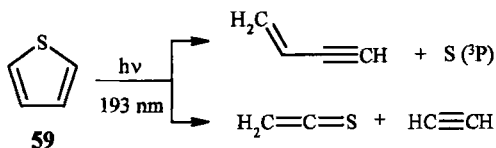
Pyrrolidine (**55**), which was studied in shock tube experiments in the temperature range 900–1400 K, was found to fragment in a way similar to that of THF (**52**) (87JPC6043). Whereas the ratio of ethene to propene in THF is about 4, in pyrrolidine it is much higher, about 20. In view of the high pre-exponential factors, it can be concluded that the fragmentation of THF and pyrrolidine proceeds via a diradical transition state rather than a concerted one. Loss of ethene is the main mode by which the molecular radical cation decomposes after electron impact ionization of **55** on path C, affording the species  $\cdot\text{CH}_2\text{—NH}^+=\text{CH}_2$ . Contrary to THF (**52**) and  $\gamma$ -butyrolactone (**53**), which both suffer  $[5 \rightarrow 3 + 2]$  fragmentation, the introduction of a carbonyl group next to the ring heteroatom in pyrrolidine (**55**), leading to 2-pyrrolidinone (**65**), induces a change to  $[5 \rightarrow 2 + 2 + 1]$  fragmentation (see Section VI).



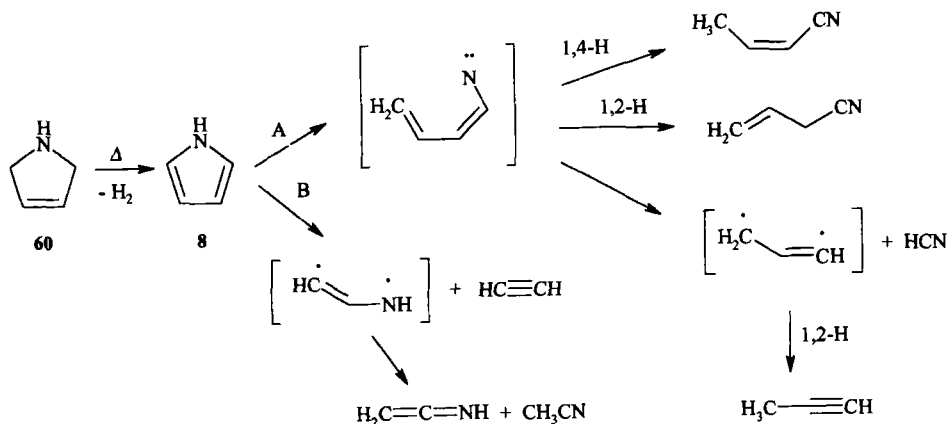
The thermal decomposition of furan (**56**) was studied in a shock tube over the temperature range 1050–1460 K (86JPC5373). For this compound also, two different  $[5 \rightarrow 3 + 2]$  fragmentations (A and B) occur, of which A, the dissociation to propyne and carbon monoxide, is the major reaction channel and much the faster. Both fragmentations are accompanied by 1,2 hydrogen migrations. Isomerizations similar to those found in pyrrole (**8**) (discussed later) were not observed.



The decomposition pattern of 2-methylfuran (**58**) is similar to that of furan (**56**) (97JPC1018). The loss of symmetry in the molecule opens more reaction channels that involve, in addition to hydrogen shift, a migration of the methyl group. The major decomposition product is carbon monoxide. Other products are  $\text{C}_4\text{H}_4$ ,  $\text{C}_2\text{H}_3$ ,  $\text{CH}_4$ ,  $\text{C}_3\text{H}_4$ ,  $\text{C}_2\text{H}_6$ ,  $\text{C}_2\text{H}_4$ ,  $\text{C}_6\text{H}_6$ ,  $\text{C}_4\text{H}_4\text{O}$ ,  $\text{C}_3\text{H}_6$ , and  $\text{C}_4\text{H}_2$ . When 2,5-dihydrofuran (**57**) is exposed to the conditions of a shock tube experiment, the main channel of pyrolysis is dehydrogenation to form furan (86JPC6011). The same dehydrogenation reaction was found to take place with 2,5-dihydrothiophene (**80**) (see Section VI) and 2,5-dihydropyrrole (**60**). For the latter compound, this reaction has also been observed under FVP conditions in the PE spectrometer (92UP1). There seem to be few reports in the literature on direct studies of the pyrolysis of thiophene (**59**) (62JA4515). However, from its mass spectrum it can be concluded that fragmentation is similar to that of furan (**56**): Loss of  $\text{C}_2\text{H}_2$  from the molecular radical cation leads to an intense peak at  $m/z = 58$ . Peaks at  $m/z = 45$  and 39 indicate fragmentation into  $\text{C}_3\text{H}_3 + \text{CHS}$ . Plasma desulfurization affords acetylene in good yields (80LA441). The photochemistry of **59** has been studied extensively (95JPC1760). Several products are formed in different yields depending on wave length and reaction conditions. The primary products of the 193-nm photofragmentation are vinyl-acetylene, acetylene, and thioketene. There are two major dissociation channels, which can be classified as  $[5 \rightarrow 4 + 1]$  and  $[5 \rightarrow 3 + 2]$ .



In the decomposition of pyrrole (**8**) in a single-pulse shock tube at elevated temperatures (1050–1450 K), a plethora of reaction products is formed, with  $\text{HCN}$ ,  $\text{CH}_3\text{CN}$ ,  $\text{CH}_2=\text{CH}-\text{CN}$ ,  $\text{C}_2\text{H}_5-\text{CN}$ ,  $\text{CH}_3-\text{CH}=\text{CH}-\text{CN}$ ,  $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CN}$ , and  $\text{CH}_3\text{CH}=\text{CH}-\text{CN}$  as major components (89JPC5802). At the low-temperature range, the isomerization products predominate (see Section III). At low temperatures propyne is the most abundant among the decomposition products without bound nitrogen. At

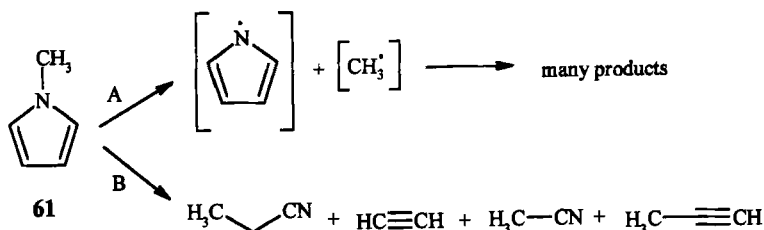


higher temperatures the isomerization products as well as propyne take part in subsequent reactions, with the formation of a large number of additional products.

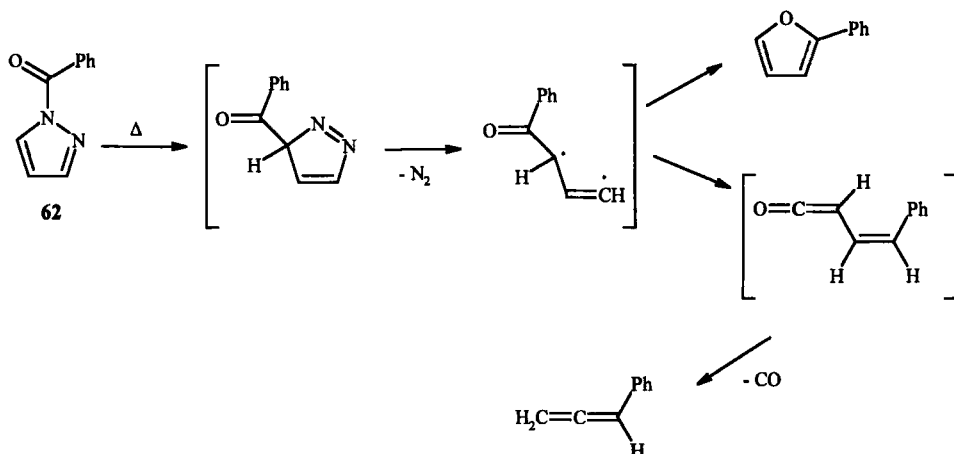
Two  $[5 \rightarrow 5]$  isomerization reactions and one  $[5 \rightarrow 3 + 2]$  fragmentation constitute the major reactions (path A). They yield *cis*-crotononitrile, propyne + HCN, and allyl cyanide, with a branching ratio of approximately 3.5:1.5:1. These three reaction channels come from a single transition structure that involves a simultaneous unimolecular C–N bond cleavage in the N-1–C-5 (N-1–C-2) position and an electronic rearrangement followed by hydrogen atom transfer. Acetylene is the second major product among the products without bound nitrogen. At high temperatures it is the product of the highest concentration. The main source for acetylene production is the  $[5 \rightarrow 3 + 2]$  fragmentation of pyrrole (path B). Electron-impact-induced decomposition was also found to proceed via this path.

A large number of decomposition products with and without bound nitrogen were obtained under shock heating (1050–1300 K) of 1-methylpyrrole (61) (93JPC4442). High concentrations of isomerization (2- and 3-methylpyrrole) and six-membered ring compounds (pyridine) were also found. The main decomposition channel (path A) is initiated by a rupture of the N–CH<sub>3</sub> bond. CH<sub>3</sub><sup>•</sup> and C<sub>4</sub>H<sub>4</sub>N<sup>•</sup>, which are formed in this process, initiate a free radical mechanism and are responsible for a plethora of products. Unimolecular ring fragmentations (path B) can be classified as  $[5 \rightarrow 3 + 2]$  reactions and afford mainly acetonitrile + propyne and propionitrile + acetylene.

A very interesting fragmentation and isomerization has been discovered for 1-benzoylpyrazole (62) (88BSB945). FVP at *ca.* 800°C affords mainly 2-phenylfuran and phenylallene, as indicated by a real-time analysis using

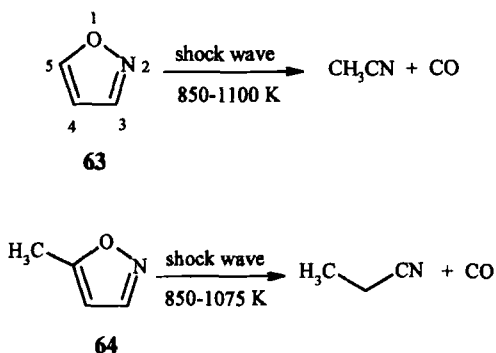


tandem mass spectrometry and by preparative scale experiments. The reaction is initiated by a [1,5] sigmatropic migration of the benzoyl group. The 3*H*-pyrazole derivatives loses  $\text{N}_2$ , affording a diradical that either cyclizes to the furan ring or rearranges to a ketene, which splits off  $\text{CO}$ , yielding the allene.

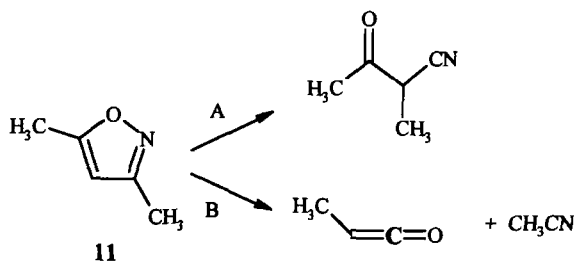


In the thermal decomposition of isoxazole (**63**), acetonitrile and carbon monoxide are the major decomposition products, followed by hydrogen cyanide, acrylonitrile, propionitrile, and acetylene (92JPC4505). Compound **63** is isoelectronic with furan (**56**) and pyrrole (**8**). Owing to the weak N–O bond in the molecule, it is expected to be kinetically much less stable than both **56** and **8** and thus decompose at much lower temperatures. It was shown that acetonitrile and carbon monoxide are obtained by unimolecular decomposition of **63**. This process takes place by a concerted N–O bond cleavage, two hydrogen atom shifts, one from position 5 to position 4, and one from position 3 to position 4, and a rupture of the C–4–C–5 bond. The overall reaction is a  $[5 \rightarrow 3 + 2]$  fragmentation. A similar fragmentation

was observed for 5-methylisoxazole (**64**) (92JPC7367), which affords propionitrile and carbon monoxide as the major decomposition products. The formation of  $C_2H_5CN$  and CO involves an N–O bond cleavage, a methyl group shift, and a rupture of the C–4–C–5 bond. This process is explained by a diradical mechanism. No isomerization products were found in the pyrolysis mixtures of both **63** and **64**.



The main thermal reaction of 3,5-dimethylisoxazole (**11**), which was studied in a shock tube over the temperature range 880–1050 K (95JPC11436), is an isomerization to 2-methyl-3-oxobutyronitrile (path A), contrary to decompositions that were found in **63** and **64**. This process involves cleavage of the N–O bond and migration of one methyl group. The feature common to all the three molecules, however, is the mode of initiation of their main thermal reaction. In all three molecules the reaction begins with an extrusion and/or cleavage of the weak N–O bond in the ring. The  $[5 \rightarrow 3 + 2]$  fragmentation of **11** leads to acetonitrile and methyl ketene (path B) (Scheme 7).



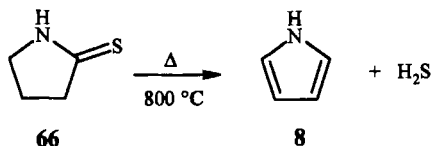
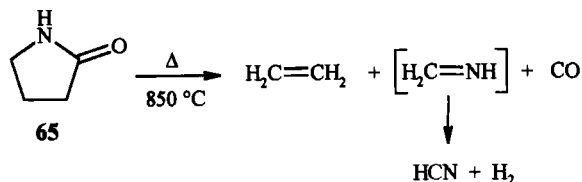
SCHEME 7



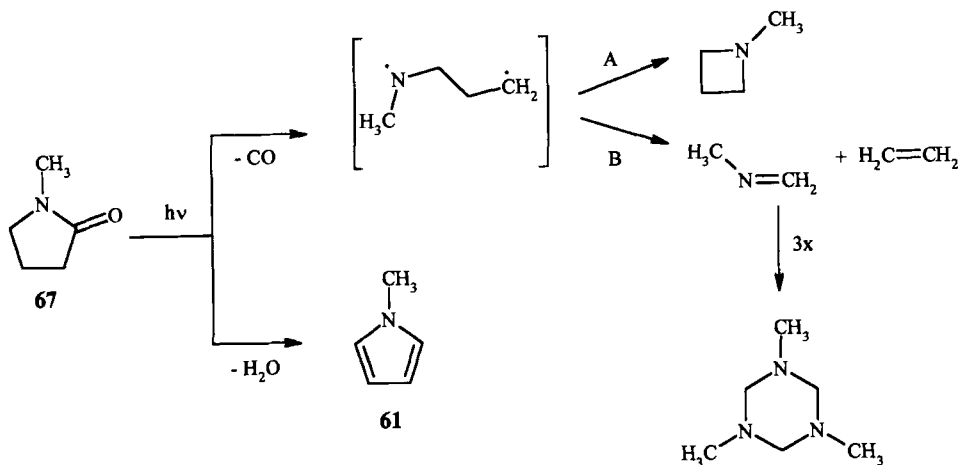
## VI. [5 → 2 + 2 + 1] Fragmentations

This type of fragmentation has been observed for a number of compounds, most of them having an exocyclic double bond. The decomposition of cyclopentanone (**3**) into ethene and carbon monoxide was described as a typical example in Section II. Cleavage of  $\gamma$ -thiobutyrolactone (**54**) into carbon monoxide, ethene, and thioformaldehyde [93JCS(P2)1249] was mentioned in Section V.E. Another typical example is the formation of atomic carbon from 5-diazotetrazole (89JA8784).

The thermal decomposition of 2-pyrrolidinone (**65**) was studied by variable-temperature PE spectroscopy [95JCS(P2)427]. The products are ethene, hydrogen cyanide, carbon monoxide, and molecular hydrogen. Methanimine ( $\text{H}_2\text{C}=\text{NH}$ ), which probably is a primary product, should be relatively stable under the reaction conditions but was not detected in the pyrolysis of **65**. Therefore, chemical activation is probably involved in the generation of this compound, as it readily decomposes into HCN and  $\text{H}_2$  at temperatures at which it was observed, in isolation, to be stable. There are several possible pathways for the fragmentation of **65** that lead to the observed products; however, ring contraction to azetidine ([5 → 4 + 1] fragmentation) can be excluded. 2-Pyrrolidinethione (**66**), which was studied by the same technique, decomposes mainly into pyrrole (**8**) and hydrogen sulfide [95JCS(P2)427]. Fragmentation of pyrrole needs more drastic conditions (see Section V.E).

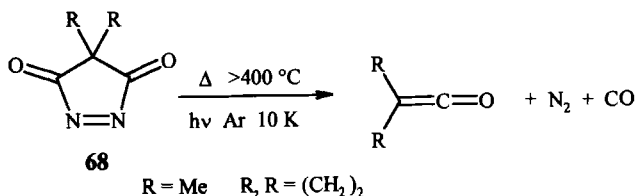


Decomposition of 1-methyl-2-pyrrolidinone (**67**) was studied by vapor-phase photolysis (72JA8281). Irradiation (Hg sensitized) led, in addition to extensive polymer formation, to the following products: carbon monoxide (31%), ethene (24%), water (24%), 1,3,5-trimethyl-hexahydro-1,3,5-triazine (8%), 1-methylazetidine (6%), 1-methylpyrrole, and methane (<1%). The mechanism of formation of most of these products involves

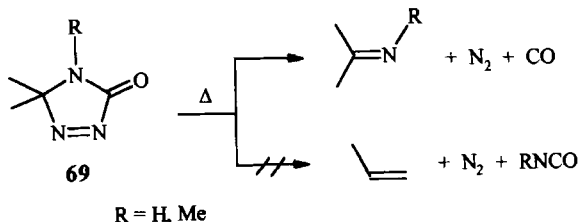


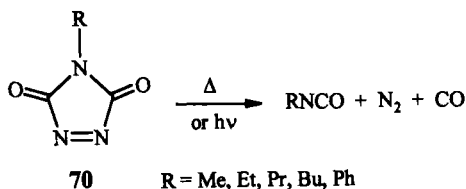
loss of carbon monoxide to give a diradical that either closes to afford the azetidine (path A) or cleaves to ethene and *N*-methylmethanimine, which trimerizes to the hexahydro-1,3,5-triazine (path B). *N*-Methylpyrrole (**61**) is formed by dehydration of **67** by a separate route.

Pyrazoline-3,5-diones (**68**) are thermally or photochemically converted to ketenes [91TL1961].



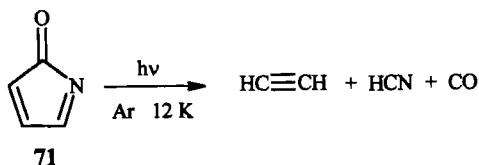
1,2,4-Triazolin-3-ones (**69**) and 1,2,4-triazoline-3,5-diones (**70**) decompose into molecular nitrogen, carbon monoxide, and an imine or an isocyanate, respectively (92TH1). The alternative fragmentation of **69** into an alkene, dinitrogen, and an isocyanate does not occur. Compounds **70** are important reagents in cycloaddition reactions [96AHC(67)119].





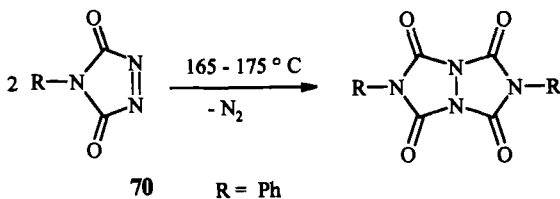
Photolysis and thermolysis of 4-aryl-1,2,4-triazoline-3,5-diones (**70**,  $R = \text{aryl}$ ) have been studied by Wamhoff and Wald (77CB1699). Photolysis produces the same products as were found in FVP. The thermal conversion of **70**,  $R = \text{Ph}$ , into the corresponding *s*-triazolo[1,2-*a*]-*s*-triazole derivative, which takes place below the decomposition temperature of the educt, is assumed to proceed via a radical chain reaction (Scheme 8).

2*H*-Pyrrol-2-one (**71**) has been studied under matrix isolation conditions (95JPC15870). It is converted photochemically into acetylene, hydrogen cyanide, and carbon monoxide.

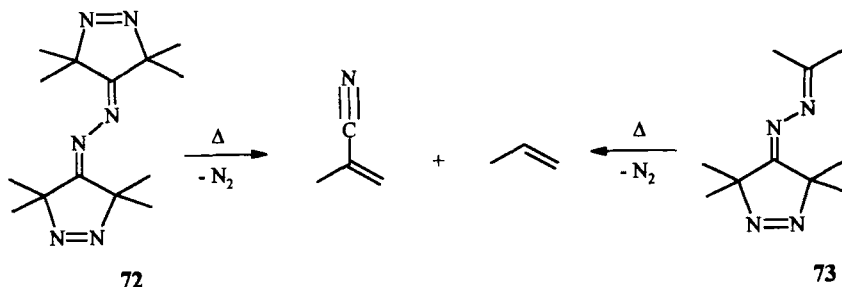


In the PES-studied gas-phase thermolysis of the azines **72** and **73** (96T1965) methacrylonitrile and propene were found in addition to molecular nitrogen, which is in accord with a  $[5 \rightarrow 2 + 2 + 1]$  fragmentation of the five-membered rings. The primary process is the cleavage of the N–N single bond, which is followed by the decay of the iminyl radicals thus formed.

Irradiation of a degassed benzene- $d_6$  solution of **72** at 90°C slowly affords a mixture of 2,3-dimethyl-2-butene and tetramethylsuccinodinitrile in almost quantitative yield together with molecular nitrogen and traces of isobutyronitrile (81TH1; 92TH2; 96T1965). The two nitriles are probably formed by dimerization and disproportionation of the  $\alpha$ -cyanoisopropyl

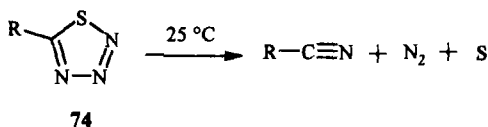


SCHEME 8



radical, respectively. This species is generated, along with 2-diazopropane, from the iminyl radical resulting from cleavage of the N–N bond.

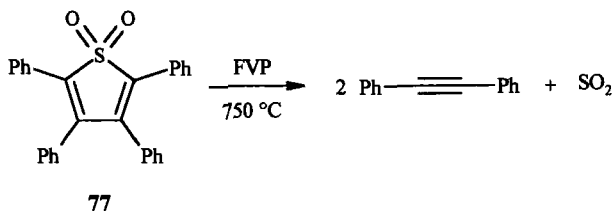
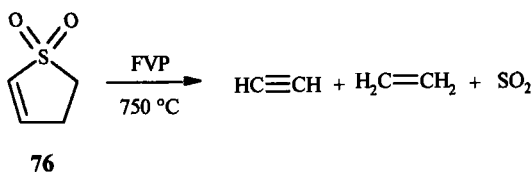
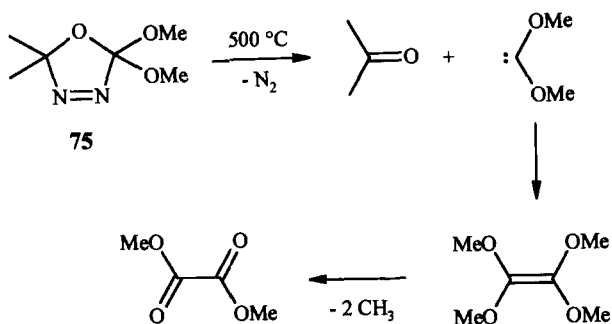
5-Substituted 1,2,3,4-thiadiazoles (**74**) easily split off dinitrogen and sulfur to afford the corresponding cyano compounds (64CB2689). Mechanistically this reaction, which has a great synthetic potential, most probably can be classified as a 1,3-dipolar cycloreversion. The rate of thermolysis depends on the substituent R and increases in the given order. 5-Aminothiadiazole (**74**, R = NH<sub>2</sub>) exploded on heating to about 100°C in the inlet system of the instrument when its pyrolysis was studied by PE spectroscopy (95UP1).



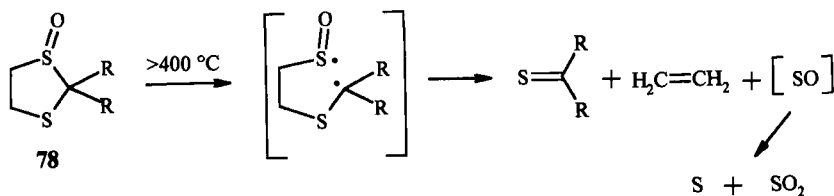
R = Alkyl, Aryl, RNH, RS, ArS, RO, ArO

Muchall *et al.* (98CC238) have recently investigated the gas-phase thermolysis of 2,5-dihydro-2,2-dimethoxy-2,5,5-trimethyl-1*H*-1,2,4-oxadiazole (**75**) by PE spectroscopy. Decomposition of **75** was induced by means of a continuous wave (CW) CO<sub>2</sub> laser as directed heat source at 26 W, which corresponds to a temperature of 500 ± 50°C. When the PE spectra of acetone, tetramethoxyethene, and dimethyl oxalate were subtracted from the pyrolysis spectrum, a simple spectrum remained that could be identified as that of dimethoxycarbene. Thermolysis in solution (94JA1161) had shown formation of tetramethoxyethene, and FVP experiments (92JA8751) gave dimethyl oxalate, both of which arise from the common precursor, dimethoxycarbene. Thermolysis of oxadiazolines similar to **75** in solution affords dialkoxycarbenes via an intermediate carbonyl ylide (94JOC5071).

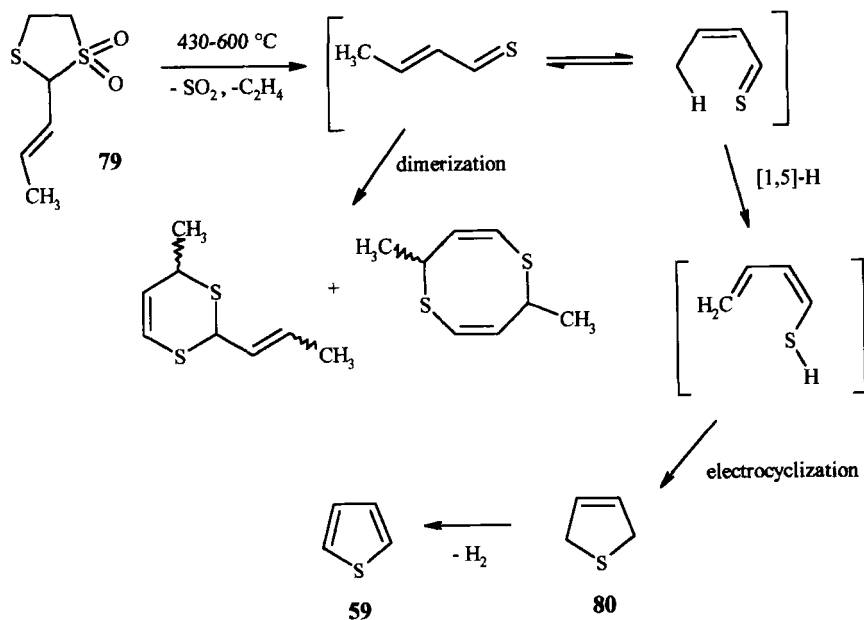
2,3-Dihydrothiophene dioxide (2-sulfolene, **76**) is partly converted to ethyne, ethene, and sulfur dioxide (93PHC1). Tetraphenylthiophene dioxide (**77**) is split to diphenylacetylene and SO<sub>2</sub> under FVP conditions, whereas solution thermolysis leads to different products (77RTC282).



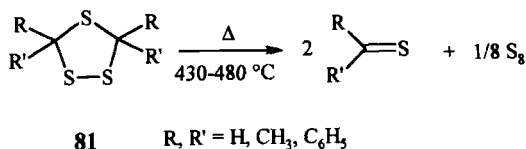
A probably stepwise  $[5 \rightarrow 2 + 2 + 1]$  fragmentation occurs in the FVP of 2,2-disubstituted 1,3-dithiolane 1-oxides (**78**), which has been investigated recently by Christensen and Holm (97AC527). The reaction products are a thioketone, ethene, and sulfur monoxide, which is known to be highly reactive, disproportionating into sulfur and sulfur dioxide [65AG437; 87AG101, 87AG(E)98]. However, only in two cases was the formation of a thioketone detected, and the full scope and limitations of this reaction remain to be clarified.

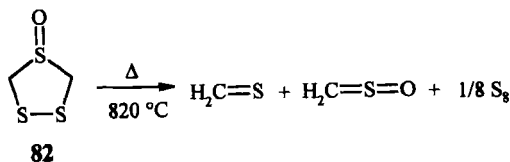


A  $[5 \rightarrow 2 + 2 + 1]$  fragmentation followed by cyclization forming a new five-membered ring was observed by FVP studies of 2-propenyl-1,3-dithiolan 1,1-dioxide (**79**) (95H1967). The reaction mixture consists of four products: thiophene (26%), 2,5-dihydrothiophene (**80**, 34%), 4-methyl-2-propenyl-4*H*-1,3-dithiine (20%), and 2,6-dimethyl-2*H*,6*H*-1,5-dithiocine (20%). The last two compounds are formed by  $[4 + 2]$  or  $[4 + 4]$  dimerization of the intermediate 2-butenethial. Formation of **80** involves a 1,5-*H* shift of the *cis*-butenethial, followed by cyclization.



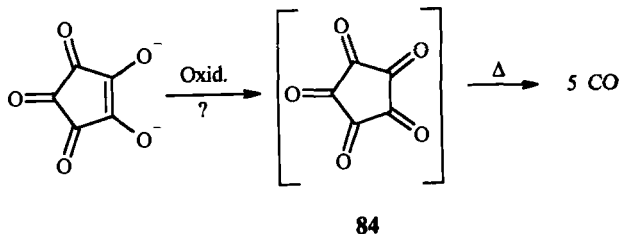
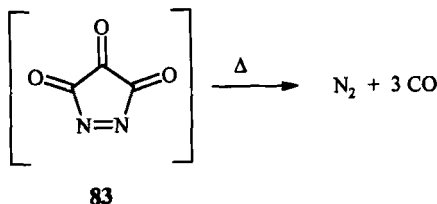
Thiocarbonyl compounds can be generated thermally in the gas-phase from a variety of precursors. Bock *et al.* [77JCS(CC)287; 82CB492] have shown that pyrolysis of 1,2,4-trithiolane derivatives (**81**) is especially advantageous for this purpose. The fragmentation reactions were monitored by PE spectroscopy. By this method thioaldehydes including thioformaldehyde and thioketones that polymerize readily were obtained. 1,2,4-Trithiolane 4-oxide (**82**) yields a mixture of thioformaldehyde and thioformaldehyde oxide.





**VII. [5 → 2 + 1 + 1 + 1] and  
[5 → 1 + 1 + 1 + 1 + 1] Fragmentations**

No real examples are known for these two types of fragmentations. Potential candidates for such a decay of a five-membered ring into four or even five fragments would be the hitherto unknown pyrazolinetriene (**83**) or cyclopentanepentaone (**84**). The latter molecule might be formed by oxidation under special conditions of its well-known precursor croconic acid (80MI2; 92CJC135; 96MI1); however, all attempts to prepare this and similar oligomers of carbon monoxide have been unsuccessful.



**VIII. Conclusions**

In the preceding sections the degradation of monocyclic five-membered ring compounds has been classified according to the fragments generated from the ring. As mentioned earlier, the course of reaction is largely determined by the number and position of double bonds, heteroatoms, and substituents. The most frequent fragmentation is of the [5 → 3 + 2] type. Mechanistically, two main types of processes can be distinguished for this

reaction, namely ring cleavage via a (diradical) intermediate that recyclizes or rearranges and 1,3-dipolar cycloreversion affording two unsaturated acyclic products, one component with a double bond and another with two cumulated double bonds or a betaine structure.

1,3-Dipolar cycloreversion was found for several, mainly the heteroatom-rich, compounds such as pentazole (**48**), tetrazoles (**38**, **46**, **47**, **48**), tetrazolines (**43**), tetrazolinones (**44**) and -thiones (**45**), 1,3,4-thiadiazolines (**39**), 1,3,4-oxadiazolidines (**42**), 1,3,4-oxathiazolinone (**40**), and 1,2,3-thiadiazole (**49**). When the compound has an exocyclic double bond, this ring fragmentation produces two compounds with cumulated double bonds.

[5  $\rightarrow$  3 + 2] Fragmentation, accompanied by ring contraction, was found for 1-pyrroline (**29**), pyrazolines (**2**, **18**, **19**, **25–27**, **31**, **35–37**), 1,3,4-oxadiazolidine (**20**), 1,3,4-thiadiazolines (**22**, **23**), 1,2,3-triazolidines (**30**, **32**, **34**), and tetrazolines (**24**, **33**). With the exception of 1,3,2-dioxathiolane 2-oxides (**21**), all these molecules have a single double bond in the ring, typically between two nitrogen atoms (i.e., they are azo compounds). Most examples are compounds with an exocyclic double bond. Such reactions are frequently explained as proceeding through a trimethylene methane-type intermediate that recyclizes either on the least-motion or on the non-least-motion path to a three-membered ring. It has, however, been shown that, at least in certain cases (e.g., **30**), such a species cannot be an intermediate but the reaction must take a different course.

In addition, there are [5  $\rightarrow$  3 + 2] fragmentations leading to acyclic products that result from the original fragments by rearrangement. Examples are 5-phenyl-1,2,3,4-thiatriazole (**50**) and related compounds with three ring heteroatoms and an exocyclic double bond (**51**), THF (**52**),  $\gamma$ -butyrolactone (**53**),  $\gamma$ -thiobutyrolactone (**54**), pyrroles (**8**, **61**), pyrrolidine (**55**), furans (**56**, **58**), pyrazole (**62**), and isoxazoles (**11**, **63**, **64**). Most of these molecules are thermally rather stable and their decomposition requires drastic conditions.

As another important mechanistic type, fragmentation into at least three products that are formed more or less simultaneously has to be mentioned. Such [5  $\rightarrow$  2 + 2 + 1] reactions were encountered in 2-pyrrolidinones (**65**, **67**), certain pyrazolidine derivatives (**68**, **72**, **73**), 1,2,4-triazolidine-3-ones (**69**) and 1,2,4-triazolidine-3,5-diones (**70**), 2*H*-pyrrol-2-ones (**71**), 1,3-dithiolane 1-oxides (**78**), 1,2,3,4-thiatriazoles (**74**), 1,2,4-oxadiazolines (**75**), and in several rings containing sulfur in an oxidized state (**76–79**, **82**). Most of these molecules have an exocyclic double bond.

Simple ring-opening reactions ([5  $\rightarrow$  5] isomerizations), which might be considered as the reversal of well-known cyclization reactions, are rather uncommon in five-membered ring compounds, and only few examples are known for unsaturated heterocycles such as pyrrole (**8**), dihydrofurans (**9**, **10**), and isoxazoles (**11**).



Sometimes it is difficult to classify the fragmentation unequivocally, in particular when short-lived, reactive intermediates that readily decompose into smaller fragments may or may not be encountered depending on reaction conditions. As examples, the oxadiazolines (**20**, **75**) can be mentioned (see Sections V.A and VI). Many reactions classified as  $[5 \rightarrow 2 + 2 + 1]$  fragmentations (Section VI) are probably initiated as a  $[5 \rightarrow 3 + 2]$  1,3-dipolar cycloreversion.

There are numerous synthetic applications of these reactions. Ring contraction of pyrazolines is a versatile method for the synthesis of three-membered rings (75MI1; 80CRV99), and  $[5 \rightarrow 3 + 2]$  cycloreversions are useful to generate special compounds with cumulated double bonds [79AG781, 79AG(E)721; 84MI3]. In particular, reactive intermediates, semi- or unstable compounds such as carbenes or carbonyl ylides (from 1,2,4-oxadiazolines like **20** and **75**), thiocarbonyl compounds (from 1,2,4-trithiolanes, **81**), thiocarbonyl ylides (from 1,3,4-thiazolines like **22** and **39**), nitrilimines (from 1,3,4-triazoles like **38**), nitrile sulfides (from 1,3,4-oxathiazolin-2-ones like **40**), and thioketene (from 1,2,3-thiadiazole **49**) have been prepared.

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